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TRIAMCINOLONE* IN RHEUMATOID ARTHRITIS

C. E. ROBINSON, M.D., and
H. S. ROBINSON, M.D.,
Vancouver, B.C.

SINCE THE POTENT anti-rheumatic properties of cortisone were first realized, many other steroid hormones have been synthesized. Several of these have been found to have greater anti-rheumatic effects milligram for milligram. Many have not been clinically useful because of their undesirable side effects which often determine whether or not a given steroid will be a practical therapeutic tool.[1] The beneficial effects, as well as the complications, of earlier steroid therapy are now well known and do not warrant reiteration.

When 9-alpha-fluoro-16-alpha-hydroxyprednisolone or triamcinolone was made available to us, we were therefore interested in assessing its anti-rheumatic potency as well as its possible side effects.

METHOD

The patients chosen were 14 ambulatory patients with rheumatoid disease. Eight of the patients were women and six were men. The ages ranged from 39 to 68 years, with an average age of 53 years. Most of the patients were in Stage III, Class II or III, of the American Rheumatism Association criteria. Eleven of the patients had classical rheumatoid arthritis, two patients had rheumatoid arthritis and associated psoriasis, and one patient had Marie-Strümpell spondylitis.

The 14 patients selected were all being managed on maintenance doses of cortisone or prednisone. Triamcinolone was substituted for the steroid, being given in an initial substitution dosage of 4 mg. triamcinolone for 5 mg. of prednisone, or for 25 mg. of cortisone. The dose of triamcinolone was then titrated until a comparable maintenance dose was achieved.

TABLE I.—CLASSIFICATION OF PATIENTS

Rheumatoid arthritis	11
Rheumatoid arthritis with psoriasis	2
Marie-Strümpell spondylitis	1
	14

Suppression of inflammatory activity was judged by:

1. Objective changes in the affected joints, including degree of swelling, heat, effusion, tenderness and joint movement, as well as changes in the sedimentation rate.
2. Subjective alterations such as the length of morning stiffness, the amount of pain and sense of well-being.

Patients were seen frequently and observed for evidence of other side effects. The blood pressure, weight, white blood cell count and differential count, sedimentation rate and hæmoglobin value were determined at intervals.

RESULTS

Ten patients were on maintenance prednisone therapy in a dosage of between 7.5 and 20 mg. daily with an average of 13 mg. These patients required triamcinolone in a dosage of from 6-16 mg. daily with an average of 10 mg. to achieve the same result. The therapeutic ratio of prednisone to triamcinolone was therefore 1.3 to 1.

The four patients on cortisone required an average of 57 mg. daily as a maintenance dose, varying from 15 to 75 mg. daily. The average maintenance dose was 8 mg. of triamcinolone, resulting in a therapeutic ratio of cortisone to triamcinolone of 9.5 to 1.

These patients have now received triamcinolone for periods ranging from two months to eight months.* While it is impossible to estimate the side effects in this short-term study, it was thought interesting to mention some of the side effects seen.

A most disturbing and perplexing effect was weight loss, which occurred in 10 patients. In these patients the loss varied from 5 to 16 lb., averaging 8.9 lb. and representing from 2-13% of the body weight. Indeed, six patients lost more than 10 lb. during the period of observation. None of these patients had visible retention of salt and

*Triamcinolone (Aristocort) for this trial was generously supplied by Lederle Laboratories Division of the American Cyanamid Company.

*Several have now been under observation for 10 months.

TABLE II.—STEROID TITRATION

No. of patients	Previous steroids	Average maint. dose	Triamcinolone Average maint. dose	Therapeutic ratio
10	Prednisone	13 mg. (7.05 - 20)	10 mg. (6 - 16)	1.3/1
4	Cortisone	57 mg. (15 -75)	8 mg. (2 - 16)	9.5/1

water before starting triamcinolone, but it cannot be denied that some of the early weight loss might have been due to diuresis, as has been reported elsewhere. The weight loss was usually rather abrupt in the beginning, with a loss of 4 or 5 lb. within a week or so; some continued to lose weight gradually over the ensuing weeks at a slower rate.

Hypertension was not a feature in any of the cases. In fact, three women, who had a mild degree of hypertension, showed a slight lowering of blood pressure while on triamcinolone. No mental side effects were noted. Headache, which is listed as one of the unusual side effects of this drug in other series, was not noted. Weakness and fatigue, prominent in 11 out of 89 patients reported by Freyberg,[2] occurred in only one of our patients.

TABLE III.—SIDE EFFECTS ON TRIAMCINOLONE THERAPY

No undesirable side effects	2
Weight loss	10
Weakness and fatigue	1
Dizziness	1
Anorexia	1
Nausea and gastro-intestinal distress	2
Purpura or ecchymosis	1
Cushingoid facies and hirsutism	2
Acute acne	1

Dizziness, requiring discontinuance of the drug, occurred in one patient. Three patients complained of anorexia, nausea and gastro-intestinal distress, though no typical ulcer symptoms developed.

Purpura, of the type frequently seen in steroid therapy, appeared abruptly in one patient on changing from prednisone to triamcinolone. This was associated with increased capillary fragility, which quickly subsided to normal on discontinuance of the drug.

Cushingoid facies and hirsutism became more marked in two patients on changing to triamcinolone, and one man developed acute acne with lesions on the face and back.

The steroid was discontinued in four patients: one because of weight loss; one because of the ecchymosis; one because of dizziness; and one because of azotæmia. This latter case will be described in more detail later.

Two of the patients mentioned, who had psoriasis in addition to their rheumatoid arthritis, improved on triamcinolone. In both instances the psoriasis involved nails as well as distal interphalangeal joints of the hands and feet; in one case it affected the skin elsewhere. The substitution of triamcinolone for prednisone caused marked improvement in the skin and nail lesions in one patient and moderate improvement in the second.

In the 14 patients there was no significant change in the levels of hæmoglobin or erythrocyte sedimentation rate on the substituted dosage of triamcinolone.

CASE REPORT

A.S., male, aged 45

This patient had a 15-year history of rheumatoid arthritis resulting in marked damage to almost all his peripheral joints and classified as Stage III, Class III. Only an apparently high pain threshold enabled him to carry on with his occupation of cab driver. A year previously he had a severe bout of upper gastro-intestinal bleeding shown to be due to a duodenal ulcer, and a subtotal gastrectomy was performed.

In January 1958, he experienced a flare-up of rheumatoid arthritis and was admitted to hospital on January 15.

His initial weight was 125 lb.; blood pressure was 120/75 mm. Hg. On admission, the hæmoglobin level was 8.7 g. %; serum proteins 5.3 g. %; albumin 2.8; and globulin 2.5 g. %. The non-protein nitrogen (N.P.N.) was 50 mg. %; the latex test was positive; his urine showed a trace of albumin; the Congo red test was negative.

After transfusion of two pints of blood the hæmoglobin level rose to 9.8 g. %.

Prednisone was started in a dosage of 5 mg. t.i.d. and he also received intra-articular hydrocortisone into the knees and one elbow. After two weeks of prednisone therapy the blood N.P.N. was 59 mg. %. Shortly after, he was changed to triamcinolone, 4 mg. t.i.d, which he continued from February 4 to March 4, 1958. He felt improved except for occasional nausea, and there was some reduction in joint swelling. His weight fell from 125 lb. to 120 lb. during the month; blood pressure varied between 140/80 and 180/90 mm. Hg. Interestingly, the blood non-protein nitrogen rose to 87 mg. % on February 18 and 95 mg. % on March 4.

In view of the increasing azotæmia he was again given prednisone, 5 mg. t.i.d., on March 4. A week later he had regained his weight. On March 12, his N.P.N. fell to 67 mg. % and on March 19 to 46 mg. %. He was discharged from hospital on maintenance doses of prednisone, 5 mg. t.i.d.

On April 15, he voluntarily stopped taking prednisone, but did not report to the out-patient clinic until one month later. On May 15, the N.P.N. was 35 mg. %; urinalysis showed albumin +++, white cells + and the occasional red blood cell. The weight was 125 lb.; blood pressure 140/80. He was again started on triamcinolone, 4 mg. t.i.d., in order to assess its effect on renal function. By June 12, his weight

had fallen to 119 lb. and the N.P.N. had risen to 78 mg. %. Prednisone therapy was therefore resumed.

This patient then, who had a borderline renal function, on being given triamcinolone alone on two separate occasions, developed a rising blood non-protein nitrogen considerably more marked than that on equivalent doses of prednisone. This was possibly due to the increased anti-anabolic or catabolic effect of this steroid, and is an interesting demonstration of the effect of steroids on protein metabolism. It is possible that his initial weight loss was due to loss of NaCl and water with contraction of his extracellular fluid compartment, thereby increasing the azotæmia.

DISCUSSION

This study confirms the anti-inflammatory effect of this newer steroid, and the results agree in general with other observations on the potency of triamcinolone compared to prednisone and cortisone.

Beyond this, the study also confirms that this steroid has new undesirable side effects, in addition to those that have been reported in other steroids.

Freyberg and others,[2] in a recent study on 89 patients receiving triamcinolone, reported some advantageous features of triamcinolone such as a lack of evidence of potassium loss. Sodium and water retention did not occur. In fact, they noted that sodium diuresis and sometimes a negative sodium balance resulted from administration of triamcinolone. They believed that this might account for some of the initial weight loss during the use of this steroid. They reported new undesirable side effects, which appeared to be peculiar to triamcinolone and which included headache; dizziness; light-headedness and sleeplessness; erythema of the face, neck, hands and forearms; nausea and indigestion; and weight loss. Weight loss of from 6-30 lb. occurred in 15 of 89 patients. This was more apparent with continued use of the drug over 90 days, and this weight loss represented up to 17% of body weight in one uncomplicated case.

Weight loss was a disturbing feature in our series of patients. While initially this may have been due to some loss of sodium and water, it is difficult to explain the continued loss of weight in some patients on this basis. It is very likely that there has been either protein loss or interference with protein formation. Metabolic studies reported by Freyberg are interpreted as indicating that this steroid can be catabolic, especially if administered in large doses for long periods.

Although osteoporosis has not been mentioned in this study, the apparent loss of protein in many patients would lead us to believe that this steroid might cause an increased incidence of osteoporosis if used over prolonged periods.

We were concerned about the possible complication of peptic ulcer which is so commonly seen with prednisone. In these 14 patients this complication was not noted. Routine barium meal examinations, however, were not done. It is interesting that three patients had already had gastrectomy performed for ulcer and one had a history of peptic ulcer which had healed. In none of these instances did the patients develop symptoms that could be interpreted as ulcer symptoms. In the series of cases reported by Freyberg, however, peptic ulcer did occur in four patients, and it would appear that this is a complication still to be reckoned with.

SUMMARY

A total of 14 patients with rheumatoid arthritis or spondylitis have received triamcinolone therapy over periods of two to eight months. In this small series of patients, disturbing weight loss, progressive in some instances, occurred in 10 patients.

It is apparent that, in addition to the well-known side effects of corticosteroids, new problems may occur with this steroid including such things as weight loss, headache, dizziness and fatigue.

Some of the new side effects described may be sufficiently severe to preclude its use in long-term maintenance dosage.

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RÉSUMÉ

La triamcinolone fut administrée à 14 malades atteints de polyarthrite chronique évolutive ou de spondylarthrite ankylosante pendant une période de deux à huit mois. On observa chez ce petit nombre de sujets une déperdition pondérale inquiétante, progressive dans quelques cas, et qui se produisit chez 10 malades. Il semble qu'en plus des manifestations réactionnelles familières du traitement aux corticostéroïdes, de nouveaux problèmes peuvent se présenter avec l'emploi de ce produit comme l'amaigrissement, les céphalées, les étourdissements et la fatigue. Quelques uns de ces incidents du traitement décrits dans le texte peuvent être assez graves pour interdire l'usage de ce médicament, même à dose d'entretien, pour une longue durée.

WINTERGREEN POISONING

"Any ingestion of methyl salicylate should be considered a medical emergency because it is so toxic. Wintergreen oil delays stomach emptying; thus gastric lavage may be used effectively up to 6 hours following ingestion and should be performed. The lack of symptoms following ingestion does not necessarily indicate a favourable prognosis. After emptying the stomach, the patient should be closely observed for the next 24 hours. In severe cases of salicylism, the use of the artificial kidney or exchange transfusion should be considered. It is hoped that in following these principles the morbidity and mortality from salicylates may be significantly reduced."—H. M. Cann and H. L. Verhulst: *J. Pediat.*, 53: 217, 1958.

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BUNDLE BRANCH BLOCK OF LONG DURATION WITH REMISSION*

SYDNEY SEGALL, M.D., F.A.C.P. and
ERROL N. SPIRA, M.D.,†
Montreal

TRANSIENT bundle branch block (B.B.B.) is not unusual. The syndrome has been ascribed to physiological, pathological and even psychological causes.[1-14] These include tachycardia, pregnancy, anæmia, anoxæmia, a variety of drugs, especially quinine and amyl nitrite, pulmonary embolism, ischæmic heart disease, myasthenia gravis, and many others. The duration of B.B.B. has almost always been shown to be short, varying from a few seconds (intermittent) to a number of weeks (transient). Where the block has been of longer duration, it has usually been assumed to be permanent. Isolated cases, however, have been reported where spontaneous remission of the B.B.B. pattern has occurred after a much longer period.[15-17]

The following cases are presented to illustrate remission of the B.B.B. pattern after permanent block had been assumed to be present for varying lengths of time.

CASE 1.—S.M., a 62-year-old man, was first seen on December 11, 1951, complaining of dyspnœa and chest pain on exertion, relieved by rest. This had been present for three to four years. There were no other symptoms. He was obese, weighing 194 lb. There were no abnormal physical findings, apart from the cardiovascular system. The arterial pressure was 194/116 mm. Hg; the heart sounds were regular and well heard. Fluoroscopy showed left ventricular hypertrophy. The E.C.G. pattern was compatible with left ventricular strain or chronic coronary insufficiency. The diagnosis of coronary sclerosis, angina pectoris, hypertensive heart disease and obesity was made, and the patient was treated with diet and modification of his activity.

On February 15, 1952, there was a fairly sudden onset of severe protracted retrosternal pain, radiating to the right shoulder and arm. Serial E.C.G.'s showed the typical evolution of postero-lateral myocardial infarction. He was treated with sedation and analgesia, and complete bed rest. Convalescence was uneventful. After ambulation, the patient continued to experience angina on effort. He was seen on August 8, 1952, when an E.C.G. showed left B.B.B. for the first time (Fig. 1). On October 22, 1952, the arterial pressure was 140/80 mm. Hg, and there were some left basal crepitations. The E.C.G. showed left B.B.B. (Fig. 1) with no significant change from the previous record. The patient was digitalized. During the next year, he was considerably improved and complained only of very occasional anginal pain. Tracings were repeated on January 27 (Fig. 1), May 5 and May 29, 1953, and continued to show left B.B.B. On August 9, 1953, there was a two-hour episode of nocturnal chest pain. The next morning the E.C.G., one year after the onset of left B.B.B., showed for the first time an intermittent block with short periods of normal conduction (Fig. 1). There were

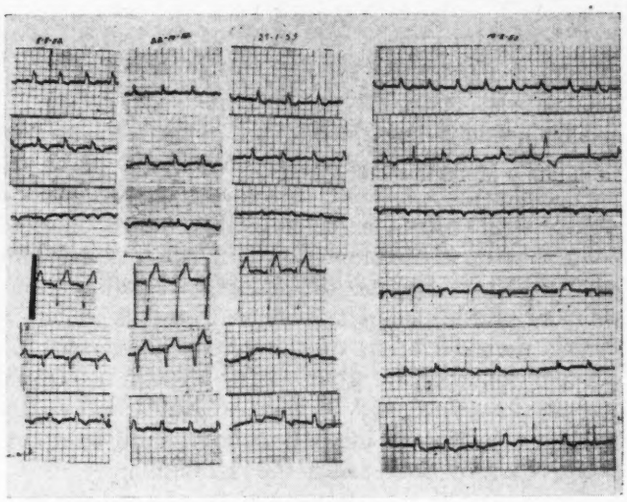

Fig. 1. Case 1.—E.C.G.'s showing left bundle branch block on August 8 and October 22, 1952, and January 27, 1953. On August 10, 1953, there is intermittent block with short periods of normal conduction.

frequent ventricular premature systoles. On October 20, 1953, two months later, an E.C.G. showed normal conduction (Fig. 2). It is of interest that evidence of old anterior wall infarction, previously undetected, was now revealed. Three days later, the patient died of a massive coronary occlusion with anterior myocardial infarction.

CASE 2.—R.S., a 50-year-old housewife doing light housework, was seen on October 16, 1950, complaining of migrainous headaches with anorexia and nausea. The patient was a known hypertensive for more than two years. The arterial pressure was 210/125. The heart was not enlarged. The aortic second sound was accentuated. Examination of the fundi revealed a grade 2 retinopathy. The E.C.G. was within normal limits. There was symptomatic improvement with treatment. On February 22, 1951, there was a slight recurrence of symptoms. The E.C.G. was unchanged. Fluoroscopy showed slight left ventricular hypertrophy. On September 7, 1951, there was no chest pain and no dyspnœa, the arterial pressure was 196/106, and the E.C.G. was unchanged. Tracings taken at regular intervals remained unchanged until November 8, 1953, when the patient, while sitting, had an episode of pressure-like chest pain lasting 10 minutes, radiating to the left shoulder and accompanied by slight dyspnœa. The patient did not see a physician at this time. She had no further symptoms, and when seen on December 8, 1953, during a routine visit, her

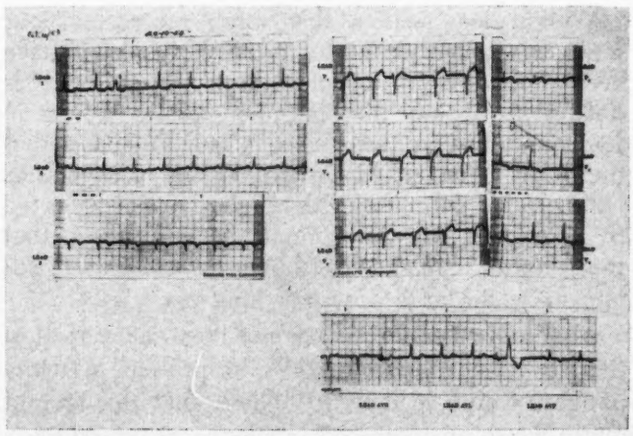

Fig. 2. Case 1.—E.C.G. of October 20, 1953, showing normal conduction.

*From the Cardiovascular Unit, Jewish General Hospital, Montreal.
†Research Fellow in Cardiology at the Jewish General Hospital, Montreal.

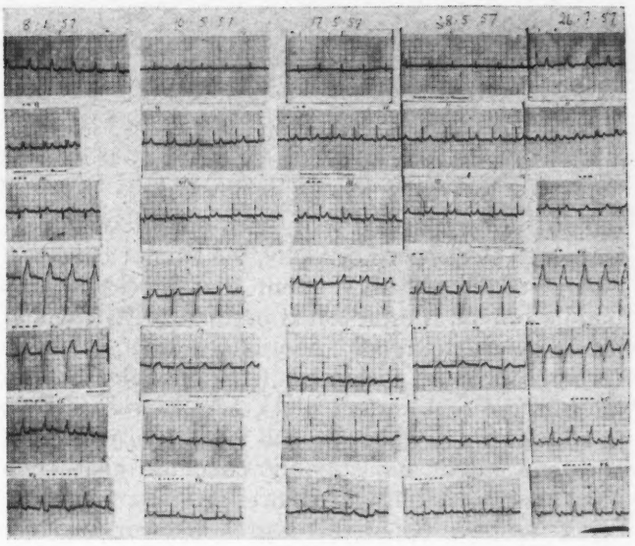

Fig. 3. Case 3.—E.C.G. of January 8, 1957, showing left bundle branch block; on May 10, 1957, normal conduction; on May 17, 1957, T-wave changes in keeping with coronary insufficiency. Normal conduction again on May 28, 1957, and left bundle branch block on July 26, 1957.

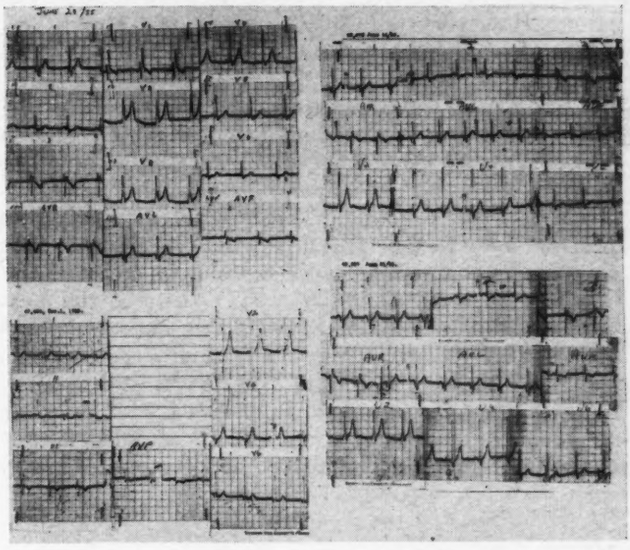

Fig. 4. Case 4.—E.C.G. of June 23, 1955, showing right bundle branch block. On December 1, 1955, normal conduction. E.C.G.'s of June 14 and June 21, 1956, again show right bundle branch block.

arterial pressure was 172/90. There were no other significant physical findings. The E.C.G. for the first time showed a right B.B.B. She remained relatively well, though she began to experience occasional episodes of chest pain, relieved by nitroglycerin. E.C.G.'s taken regularly from May to December 1954 and in May, June, July and October 1955 and January 1956 continued to show right B.B.B. The arterial pressure appeared to be under control at 140/80, with reserpine. On April 6, 1956, she had been complaining of oppressive substernal discomfort for a week. On examination, the arterial pressure was 136/72. The E.C.G. no longer showed the right B.B.B. and was within normal limits. Another E.C.G. in July 1956, however, again showed the right B.B.B. Although the patient has had no angina or other symptoms since, the right B.B.B. appears to have persisted.

CASE 3.—G.M., a 63-year-old carpenter, was admitted to hospital with psychogenic complaints in December 1956. An E.C.G. in hospital showed left B.B.B., and he was told that he had some heart disease. On January 8, 1957, after discharge from hospital, he consulted one of the authors about his heart, though he had no symptoms. Examination revealed arterial pressure of 126/70, the heart was not enlarged and the E.C.G. again revealed left B.B.B. (Fig. 3). During the next four months he was well. E.C.G.'s on January 18, February 5, and March 1, 1957, continued to show left B.B.B. During the night of May 6, 1957, he awoke with a localized precordial ache, which lasted about half an hour. He was examined five days later. There was no change in his condition, but an E.C.G. at this time was normal (Fig. 3). The left B.B.B. had disappeared. One week later, the E.C.G. (Fig. 3) showed T-wave changes in keeping with coronary insufficiency, probably related to the episode of May 6, 1957. During the next two months, two tracings showed normal conduction (Fig. 3 (28.5.57)) and he was asymptomatic. On July 26, 1957, he felt well, had no symptoms and the arterial pressure was 110/70. However, a routine E.C.G. once again showed left B.B.B. (Fig. 3) which has persisted since.

CASE 4.—A.B., a 53-year-old garment worker, was seen on May 14, 1953, complaining of typical angina pectoris, relieved by nitroglycerin. His arterial pressure was 170/80, and the E.C.G. was normal, though with high voltage T-waves in V_2 and V_4. Records taken in June, July, October and November of 1954 were all within normal limits. On June 23, 1955, without any significant clinical change, the E.C.G. showed right B.B.B. (Fig. 4). On December 1, 1955, the B.B.B. was gone (Fig. 4), but six months later, on June 14, 1956, it was again present (Fig. 4). Two further E.C.G.'s in 1956 again showed B.B.B. By February 1957 (Fig. 5) the attacks of angina were becoming more frequent, with a definite decrease in effort tolerance, and in the next month he was forced to give up his work. During March, the patient had an episode of severe nocturnal chest pain, but he disregarded this, blaming it on some food he had

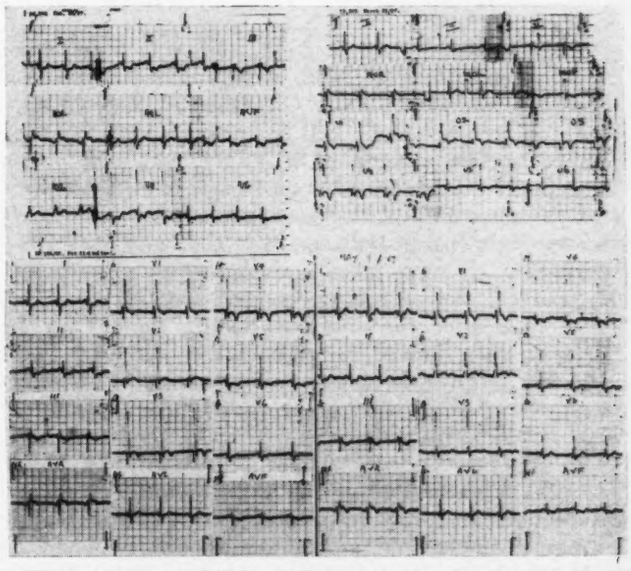

Fig. 5. Case 4.—E.C.G. of February 28, 1957, showing right bundle branch block. Tracings of March 14 and March 29, 1957, suggest anterior myocardial infarction, in the presence of right bundle branch block. On May 9, 1957, right bundle branch block is still present, but significant Q-waves have disappeared.

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eaten. However, an E.C.G. taken on March 14, 1957, showed a significant Q-wave, with T-wave inversion in V_3 to V_6 (Fig. 5). Five days later, another E.C.G. continued to suggest the typical evolution of anterior myocardial infarction, superimposed on right B.B.B. On March 26, 1957, he was admitted to hospital because of an attack of severe chest pain, associated with sweating. The arterial pressure was 110/60. Two further E.C.G.'s while in hospital were considered compatible with anterior myocardial infarction (Fig. 5—March 29, 1957). During the next three months, he felt much better, with improved effort tolerance. A record in May 1957 (Fig. 5) and one in July 1957 showed that right B.B.B. was still present, but significant Q-waves had disappeared. Less than one month later, on August 8, an E.C.G. revealed normal conduction (Fig. 6). The B.B.B. had disappeared after

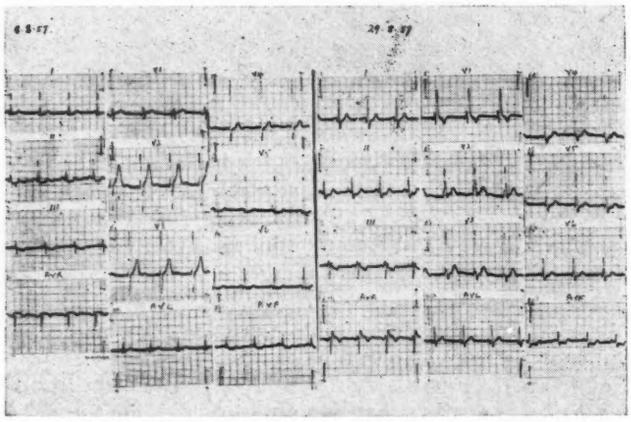

Fig. 6. Case 4.—Normal conduction on August 8, 1957. E.C.G. of August 29, 1957, again shows right bundle branch block.

having been present for a period of 14 months, and there was no evidence of infarction. Three weeks later, while effort tolerance continued to improve, the E.C.G. once again showed right B.B.B. (Fig. 6). He has since continued to oscillate between normal conduction and right B.B.B., with no significant change in his symptoms.

CASE 5.—H.G., a 63-year-old man, was hospitalized in April and May of 1952, with anterior myocardial infarction. On May 6, an E.C.G. showed the infarction and a pattern of right B.B.B. In July 1952 he complained of substernal pain on effort. Although underlying heart disease was known in this man, there were strong suggestions of cardioneurotic overlay. An E.C.G. showed right B.B.B. Between May 1952 and May 1953, seven E.C.G.'s were taken and all showed right B.B.B. The clinical picture was unchanged. On July 15, 1953, 14 months after the onset of B.B.B., the E.C.G. for the first time showed no right B.B.B. although there was some intraventricular conduction defect. Two weeks later, the B.B.B. was again present, and again on August 6, 1953. On October 15, 1953, there was once again normal conduction, and the record on March 11, 1954, also showed normal conduction. The normal conduction and the relatively good clinical picture continued unchanged until May 26, 1954, when he complained of some intermittent chest pain; an E.C.G. taken at this time showed that the block had returned. In October 1957, it was still present, having been regularly demonstrated in E.C.G.'s taken at the times of this man's very frequent visits. The clinical picture has remained one of complaints of intermittent pains, though with much neurotic overlay.

DISCUSSION

Before discussing the aspects of these cases, it should be emphasized that, with our present techniques of electrocardiography, we cannot conclude unequivocally in any patient that blockage of a bundle branch is established permanently. It would be necessary to record continuous tracings to be certain. In some instances, it is possible that an intermittent or transient block may be recorded at just those times when the B.B.B. pattern is present and one might unjustifiably conclude that such blocks were established. Hence, in discussing these cases, we have borne this source of error in mind.

A striking but well-known aspect of the cases observed was the lack of correlation between the B.B.B. and the prognosis. Case 1 reverted to normal sinus rhythm just a few days before he died of a second large infarction of the myocardium. Cases 2, 3 and 4 all had fairly severe myocardial damage, associated with the B.B.B., but all cases reverted to normal conduction for various lengths of time. These periods were not associated with any significant change in the clinical pictures nor was there any clinical change for the worse when the B.B.B. recurred. Case 3 actually showed a reversal to normal conduction at a time when clinical history and S-T and T-wave changes suggested acute coronary insufficiency with myocardial ischæmia. Case 5, in a man with known myocardial damage and B.B.B., acquired at the time of his infarction, retained the block pattern for almost 14 months. There was then intermittency, followed again by a short period of B.B.B. The E.C.G. showed normal conduction for more than seven months, during a period that was almost symptom-free. The B.B.B. pattern then recurred, although there was no remarkable change in symptoms or signs.

Attempting to explain these remissions in the B.B.B. patterns, one can postulate that the conducting tissue is either incompletely damaged in the first place or is capable of considerable regeneration. The latter theory seems largely untenable in the light of past observations and in view of the ultimate reversion to impairment of conduction in all these cases, with the exception of Case 1, where death intervened presumably before the B.B.B. pattern could again be recorded. It therefore seems likely that the conduction tissue was incompletely damaged in the first place, while slow and clinically undetectable extension of involvement was occurring. It may be added that other factors of a physiological nature, such as compensatory collateral circulation, better oxygenation of the myocardium and reduction in physical activity, were possibly responsible for the periods of remission.

In conclusion, it should be stressed that bundle branch block, even when apparently permanent for

more than a year, cannot be considered as definitely established. The transiency of the block may be missed by too infrequent E.C.G.'s, or one may be dealing with a case which, at some future time, may revert to normal conduction. Finally, the presence or absence of bundle branch block has little bearing on prognosis and, in fact, may be misleading to the unwary clinician.

SUMMARY

Five cases of transient B.B.B. have been presented.

The block was present in all cases for an unusual length of time before remission occurred. Normal conduction appeared in Case 2 after the B.B.B. had been present for 28 months; in Cases 4 and 5, after 14 months; in Case 1, after 12 months; and in Case 3, after at least 5 months, although the actual date of onset in this patient was not known.

In all cases, with the exception of Case 1, in which death occurred three days after the demonstration of normal conduction, the block pattern tended to recur at a varying interval of time after remission of the block.

No correlation was found between the severity of the disease or the prognosis, and the presence or absence of block.

The assumption that B.B.B. is permanent should always be made with reservation.

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RÉSUMÉ

Les auteurs présentent cinq cas de bloc temporaire des branches du faisceau de His. Dans chaque cas, cette anomalie avait persisté pendant une durée inusitée avant que la transmission normale ne se rétablisse. Dans un cas ce délai s'étendit à 28 mois; dans deux autres, à 14 mois; et à 12 et à au moins cinq mois dans les autres cas. Chez tous les malades dont les faits cliniques sont fournis (sauf pour un qui mourut trois jours après le rétablissement de la transmission normale) le bloc de branche s'installa de nouveau après certains intervales de transmission normale.

On ne peut établir aucun rapport entre la gravité de la maladie, le pronostic et la présence ou l'absence de dissociation auriculo-ventriculaire. Il faut donc toujours observer la plus grande prudence avant de déclarer qu'un bloc de branche s'est installé de manière permanente.

SIMPLE MASTECTOMY AND POSTOPERATIVE IRRADIATION FOR CARCINOMA OF THE BREAST
A REPORT FROM THE SAINT JOHN GENERAL HOSPITAL*

J. A. CASKEY, M.B., Ch.B., D.M.R.T.,
Saint John, N.B.

FEW SUBJECTS in medicine have aroused so much controversy as the treatment of carcinoma of the breast. One of the main issues has been the relative merits of the radical operation as against simple mastectomy and postoperative radiotherapy. The leading protagonists of the radical operation have spoken against those performing less radical surgery with all the vehemence of a political campaign. Unselected results from centres employing the radical operation are such that no one can justly be condemned for investigating some other method of treatment.

Fuel is continually added to the fires of confusion by the publication of statistical data which are often inaccurate and, more important, from which quite false conclusions are drawn. Because medical men seek to convince their colleagues by the publication of such data and conclusions, it would seem justifiable to suggest that a national statistical group should be available and that no statistical article should be accepted by any journal until it has been submitted to this statistical group for assessment. All conclusions drawn from such statistics should also be subject to approval by the group. In this way the reader would have at least partial assurance of the degree of validity of any article.

Recently MacLean[1] published a five-year survival rate of 47.5% for cases treated in the Winnipeg General Hospital between the years 1940 and 1949. He compared this survival rate with that published by McWhirter[2] who, by routine simple mastectomy and postoperative irradiation, obtained a crude survival rate of 42%. MacLean's published cases were predominantly treated by radical mastectomy, and he stated: "This 5.5% increase in salvage rate by the more radical procedure is significant, and in our opinion demonstrates the superiority of radical mastectomy over simple mastectomy and radiation as the therapy of choice for operable breast cancer." Such a conclusion based on his published figures could be false, which the figures themselves prove. MacLean showed an operability rate for the radical operation of 83.5%, whereas in the Edinburgh series only 57% were in the operable group. MacLean was therefore endeavouring to compare two

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dissimilar groups of patients, his own showing a much greater proportion of early cases.

Watson[3] published an excellent article in 1957 giving unselected data for all cases of carcinoma of the breast seen in Saskatchewan from 1944 to 1949. However, with a total of 629 cases his annual incidence was 21 per 100,000 females. Even adding previously treated cases seen during this period, his incidence is still only 34 per 100,000 females; in many other centres the incidence is much higher, in the region of 50 per 100,000 females; the New Brunswick incidence for the period 1954 to 1956 was 46 per 100,000 females. Watson's opinion regarding treatment is based on an extremely low incidence for the geographic area; in view of this, can any valid statistical comparison be made with another centre?

TABLE I.—MARBLES EXPERIMENT

	Stage I	*Stage II*	*Stage III*	*Stage IV*	*Overall*
Dr. A.....	59%	26%	20%	0%	34%
Dr. B.....	80%	54%	27%	11%	34%
Correct assessment...	64%	38%	20%	1%	34%

The same "patients" staged by two examiners:
0 - 5 marbles—Stage I
6 - 10 marbles—Stage II
11 - 15 marbles—Stage III
16 - 20 marbles—Stage IV

Those who seek to prove their points by quoting survival figures for operable cases only, or for certain stages, also add to the chaos. In 1955, Batley[4] published the results of an interesting experiment illustrating the fallacy of comparing cases assigned to stages by different individuals. Batley took 20 sand-bags and in each placed a different number of ordinary marbles. He allocated a survival rate to each bag depending on the number of marbles and then grouped the bags in four stages as shown in Table I.

Two experienced examiners were then asked to palpate the bags and decide how many marbles each contained and so allocate each bag to one of the four stages. The difference in survival rate obtained by each examiner in each stage is shown in the top two lines of Table I. The overall or crude survival rate is, of course, the same for both Dr. A. and Dr. B. Dr. B. has obtained his better results by being more conservative in his staging than Dr. A.

It is our opinion that survival figures for breast cancer cannot be compared between different centres. The infinite variations in composition of the cases, in clinical and pathological assessment and in treatment methods, both surgical and radiotherapeutic, render such comparisons invalid. In comparing the efficacy of two different methods of treatment, the nearest approach to statistical reliability is to compare these two methods in the same centre which must serve a geographic area. The only variable is then in the patients; all other variables can be kept constant. This comparison may be made by random selection if the volume is large enough or by comparison of different quinquennia. Any attempt to match like cases from different centres brings in all the other variables and must therefore be less reliable.

At the beginning of 1952, the staff of the Saint John General Hospital decided to apply, wherever possible, the plan of simple mastectomy and postoperative irradiation to all cases of breast carcinoma referred to the hospital. The technique to be followed was identical to that of McWhirter in Edinburgh. It was realized at the time that this change of policy would have to be made by all surgeons, or no useful results would be forthcoming. At the same time many surgeons in other parts of the province adopted the same policy, but some continued to perform the radical operation, so our figures include these cases.

TABLE II.—SURVIVAL RATE IN ALL CASES OF BREAST CARCINOMA, SAINT JOHN GENERAL HOSPITAL, 1952-56

	1952	*1953*	*1954*	*1955*	*1956*
Cases (Total 257)....	42	50	50	48	67
1 year.....	86%	88%	84%	94%	82%
2 years.....	76%	76%	70%	75%	
3 years.....	66.5%	56%	60%		
4 years.....	59.5%	50%			
5 years.....	57%				

It is emphasized that the cases reported are all the cases seen at the Saint John General Hospital, treated or untreated, and all deaths are attributed to cancer even though post-mortem examinations in several cases revealed no evidence of malignancy. Our follow-up has been 100% with no untraced cases. The average age was 55.9 years, the oldest patient being 94 and the youngest 24.

Table II shows the survival rate for the 257 cases seen between 1952 and 1956. This survival table was compiled to give us our first year's five-year survival and to show the trend in the subsequent years. The figure of 57% five-year survival for the 1952 cases is probably higher than the average will be for the subsequent years, but from the trend it would appear that it will not be too far below 50%. However, this is a preliminary report which shows a satisfactory trend.

TABLE III.—FEMALE BREAST CARCINOMA, SAINT JOHN GENERAL HOSPITAL, 1952-1956

Stage I		*Stage II*		*Stage III*		*Stage IV*	
133	52%	57	22%	19	7.5%	48	18.5%

The composition of the 257 cases according to the Manchester classification is shown in Table III. In the plan of simple mastectomy and postoperative irradiation, no axillary tissue is available for histological study and it is therefore probable that the proportion between stages I and II would vary

slightly had stages been determined after radical excision. However, the grouping between operable and inoperable appears approximately similar to that reported in other Canadian provinces. In our grouping within the stages we have a relatively high proportion of stage I and a low proportion of stage III cases. It must be borne in mind that many stage I cases pass directly to stage III, and it is probable that the earlier patients report to their physician the greater will be the proportion of stage I as opposed to stage III cases.

Of the 257 cases 202 (79%) were treated by simple mastectomy and postoperative x-ray therapy, 27 (10%) by radical mastectomy and postoperative x-ray therapy, and 28 (11%) had either palliative x-ray therapy only, hormones, or no treatment.

TABLE IV.—SURVIVAL RATE OMITTING CASES TREATED BY RADICAL MASTECTOMY

(SURVIVAL RATE FOR ALL CASES SHOWN IN BRACKETS)

	1952	*1953*	*1954*	*1955*	*1956*
Cases	35 (42)	50 (50)	37 (50)	47 (48)	61 (67)
1 year					80.5% (82%)
2 years				76% (75%)	
3 years			59.5% (60%)		
4 years		50% (50%)			
5 years	57% (57%)				

The survival table with the cases treated by radical mastectomy subtracted shows virtually no difference from that of the whole group. The few cases treated by radical excision were all early cases.

In the plan of simple mastectomy and postoperative irradiation, it is still not universally appreciated that the surgical operation must be performed according to certain rules in order that radiotherapy may be given in full radical dosage, and to the whole operative area.

In some of our cases, the simple mastectomy had been performed in a manner which rendered subsequent radical radiotherapy impossible. Tense flaps, burst wounds, and long transverse scars have been the main offenders. Tension in skin flaps leads to poorer blood supply and consequently a poorer response to radiotherapy. Long transverse scars and wide undercutting often mean that some of a potentially contaminated area must be left unirradiated.

The main prerequisites of the operation are:

1. As short a scar as possible, placed as nearly vertically as is consistent with the site of the tumour.

2. *The skin flaps must come together without tension.* This necessitates a careful estimate before the ellipse of skin is incised round the areola. No tension sutures should be necessary.

3. The pectoral fascia is left intact if uninvolved. If it is involved, the area of involvement together with the underlying portion of muscle is removed.

4. The axilla is not dissected. Palpable lymph nodes are left *in situ.*

5. No stab drain is put in the axilla. A small piece of rubber dam is put in the lower end of the wound. Transverse scars are not only too large in many cases for adequate radiotherapy, but they give a much greater liability to fluid collections deep to the lower flap.

6. Adhesives should not be used for anchoring dressings. They markedly increase the skin reaction.

Radiotherapy is commenced during the second postoperative week and is given in 15 treatments over a three-week period. All fields are treated each day. A dosage of 3750 r is given centrally between two large opposed 25 cm. x 12½ cm. or 25 cm. x 10 cm. fields, treating the axilla and supraclavicular region. The same dosage is given centrally between two glancing fields to the breast area.

In some patients with thick shoulders, the central dosage in the axilla and supraclavicular region falls below 3750 r because of limitation of skin tolerance. From our 1952-1954 cases we extracted those who were treated radically by simple mastectomy and postoperative radiotherapy. We then divided the resulting cases into those receiving a dose of 3750 r centrally in the axilla and those receiving less than this dose, and noted the three-year survival in each case.

TABLE V.—THREE-YEAR SURVIVAL RATE—CASES TREATED RADICALLY BY SIMPLE MASTECTOMY AND POSTOPERATIVE THERAPY, SAINT JOHN GENERAL HOSPITAL, 1952-1954

Axillary and supraclavicular tumour dose 3750 r or over		*Under 3750 r*	
60/77	78%	11/24	46%
	Cases under 65 years		
50/63	79.5%	4/14	28.5%
	Stage I cases		
41/46	89%	3/4	75%
	Stages II, III and IV		
9/17	53%	1/10	10%

Table V shows the results of this investigation. As can be seen, the survival rate in those reaching full dosage is higher than in the group who do not reach full dosage. As older patients are more liable to die of intercurrent disease, we then subtracted all cases in patients over 65 years of age. When only those under 65 are considered, the difference is even more marked. In stage I cases, as would be expected, the difference is less marked, and in the remaining stages II, III and IV, the greatest difference is seen.

In all these cases the technique of treatment and the overall time were the same. The only variation was in dosage and in thickness of the patient. If dosage is responsible for this difference, and if this difference is maintained in later survival figures, it will disprove McKinnon's[5] claim that no form of treatment has any influence on breast cancer. McWhirter has also published figures showing differences in survival with different dosage. We shall

not be able to continue a study of this dosage effect, for we now treat the shoulder region by cobalt teletherapy, and in radical treatment almost all cases can be given the prescribed dose without exceeding tissue tolerance.

SUMMARY

In this paper we have endeavoured to point out some of the difficulties encountered in comparing data between different centres. We have suggested that rather than perpetuate useless argument based on invalid comparisons, each centre with adequate surgical and radiotherapy services should make its own comparison of the two different methods of treatment.

We have presented a preliminary report on unselected cases of breast carcinoma seen at the Saint John General Hospital between 1952 and 1956. The overall survival rate in these cases has, up to the present, justified the policy of our surgical team in abandoning the radical operation in favour of simple mastectomy and postoperative irradiation.

Table I is reproduced with the kind permission of Dr. Frank Batley.

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RÉSUMÉ

Un des plus grands obstacles au choix de la meilleure forme de traitement du cancer du sein est sans doute la difficulté de comparer les résultats obtenus dans différents centres de traitement. L'auteur suggère qu'au lieu de perpétuer une discussion oiseuse fondée sur des comparaisons insoutenables, chaque centre possédant des services de chirugie et de radiothérapie bien organisés devrait établir ses propres comparaisons entre la mastectomie élargie avec curage ganglionnaire et la mastectomie simple suivie de radiothérapie. L'auteur a présenté ses données préliminaires tirées d'une série de malades traités à l'Hôpital Général de Saint-Jean entre 1952 et 1956. La survie totale dans ces cas jusqu'à présent a justifié ses collègues de chirurgie d'abandonner la résection large pour adopter à la place la mastectomie simple suivie d'irradiation post-opératoire.

ILEOCYSTOPLASTY*

A. H. IRVINE, M.D., F.R.C.S.[C], *Ottawa*

THE USE of an isolated segment of small bowel for replacement of a portion of ureter or in reimplantation of ureter into bladder is today an accepted surgical procedure. The purpose of this article is to report two examples of ileocystoplasty carried out in patients having solitary kidneys.

CASE REPORTS

CASE 1.—B.F., a white man, was first seen in January 1945, at the age of 21 years. He complained of transient gross hæmaturia after a fall in which he sustained a blow to the abdomen. There was no previous history of disease referable to the urinary tract. Investigation revealed bilateral hydronephrosis and hydroureters secondary to strictures at the uretero-vesical junction.

These strictures were dilated on several occasions during 1945, with some early improvement. Over the following two years, however, there was a progressive increase in hydronephrosis, particularly on the left side. A left uretero-vesicoplasty was performed in October 1947. This was followed by repeated bouts of left-sided pyelonephritis and nephrolithiasis. Reimplantation of the right ureter into the bladder was carried out in January 1949. In April of that year a left perinephric abscess was drained, and the left kidney was removed one month later. A severe stricture developed at the reimplantation site, and right nephrostomy was done in July 1949.

The nephrostomy tube was changed at approximately monthly intervals for the ensuing nine years. During this period he had numerous episodes of acute pyelonephritis, often requiring treatment in hospital. In 1955, it was suggested to the patient that an ileocystoplasty be done but he preferred not to have any further surgery carried out. Three more hospital admissions for infection in the next two years finally caused him to change his mind and he was brought into hospital in February 1958.

Examination showed the patient to be in good general condition, though somewhat underweight. Non-protein nitrogen (NPN) level in serum was 28 mg. %. Urine contained 10-15 pus cells per high power field (H.P.F.) and protein content was one-plus. Urine culture grew *A. aerogenes, B. coli* and a non-hæmolytic streptococcus.

Intravenous pyelography revealed gross hydronephrosis and hydroureter with poor concentration of dye, particularly in the upper group of calyces. Injection of the nephrostomy tube with dye outlined the dilated calyces and a large ureter which was completely stenosed at the vesical junction. The superior calyces were again poorly visualized because of the position of the nephrostomy tube which apparently interfered with both filling and drainage of this area. A series of rapid exposures were made with the ureter filled with dye, in an attempt to detect the presence of peristalsis, but none was demonstrable. Cystography outlined a small bladder with no reflux into the right ureter. A cystometrogram revealed a bladder capacity of 90 c.c. with an apparently adequate voiding contraction.

One week of tidal irrigation failed to alter the vesical capacity, and so cystoscopy under general anæsthesia was performed with dilatation of the bladder to 200 c.c.

On February 15, 1958, an ileocystoplasty was carried out. An isoperistaltic end-to-end anastomosis of a 12 inch (30 cm.) isolated segment of ileum was performed proximally to the dilated ureter about one inch

*From the Department of Urology, Ottawa Civic Hospital, Ottawa.

(2.5 cm.) below the lower pole of the kidney. Distally, it was joined end-on to the full thickness of the bladder through a circular defect in the fundus 3 cm. in diameter. Both anastomoses and the majority of the intervening bowel were extraperitonealized. The bladder was drained by an indwelling urethral catheter. The nephrostomy tube was left in place just proximal to the bowel segment.

The immediate postoperative course was quite uneventful. During this period, x-ray studies were carried out. Dye injected through the nephrostomy tube showed vigorous peristalsis in the isolated loop and free passage across the proximal and distal anastomoses. Dye was also injected into the bladder through the urethral catheter. No reflux occurred when up to 150 c.c. was introduced.

On removal of the urethral catheter the patient voided frequent small amounts with a poor stream for several hours, followed by the development of general malaise and a rise in temperature. The catheter was reinserted and the febrile episode allowed to resolve. One week later the trial was repeated, with a similar unsuccessful result. It was not known at this point whether his inadequate voiding was due to massive reflux or bladder neck obstruction or whether the patient had "forgotten how to void" in the nine years during which urine had been diverted from his bladder. Cystoscopy revealed a contracted bladder neck, and a transurethral resection was performed, removing 3 grams of tissue. After this, the patient was able to void freely with a good stream and full control.

The nephrostomy tube was clamped for a period with continued satisfactory voiding, and then removed. It was necessary to curette the nephrostomy tract under local anæsthesia to speed its closure.

When the patient was re-examined three months after operation, he was in excellent health; NPN, CO_2 combining power and serum electrolytes were normal. He voided at two-hour intervals by day and twice nightly while on a high fluid intake. An intravenous pyelogram showed persistence of the hydronephrosis but definite increase in concentration of dye, particularly in the upper group of calyces (Fig. 1).

It was noted on this follow-up visit that, by voiding a second time two or three minutes after finishing, he was able to pass a further 30 to 120 c.c. and a double voiding regimen was instituted. At present he continues to maintain a high fluid intake and voids at 4-hour intervals by day and once or twice nightly. He has passed as much as 600 c.c. at a single voiding. His urine is not yet sterile but he has had no flare-ups of infection. He is being kept on long-term sulfonamide therapy.

CASE 2.—W.M. sustained a gunshot wound to the abdomen in 1945 at the age of 20. The missile entered through the buttock and caused a rupture of the urinary bladder and terminal ileum. The bowel perforation was closed, as was the bladder, and suprapubic drainage was maintained for six weeks. He was next seen in 1948, complaining of left loin pain. Investigation revealed a non-functioning right kidney, with pyelonephritis and a staghorn calculus in the left kidney. Treatment was conservative. He was readmitted in 1950 with a recurrence of pyelonephritis. The following year he presented with a left perinephric abscess. This was drained and, while in hospital, a nephrolithotomy was performed, with incomplete removal of the calculus from the bifid left kidney. Subsequent investigation revealed an ureterovesical stricture and the ureter was reimplanted into the bladder. In 1952, a perinephric abscess drained spontaneously. After one year a stricture had developed at the site of reimplantation and was dilated. Later that year a perinephric abscess was drained. In 1955 and 1956, abscesses were drained from the prostate and scrotum. In February 1958, he was admitted to hospital once more, at which time the fourth perinephric abscess was incised and drained.

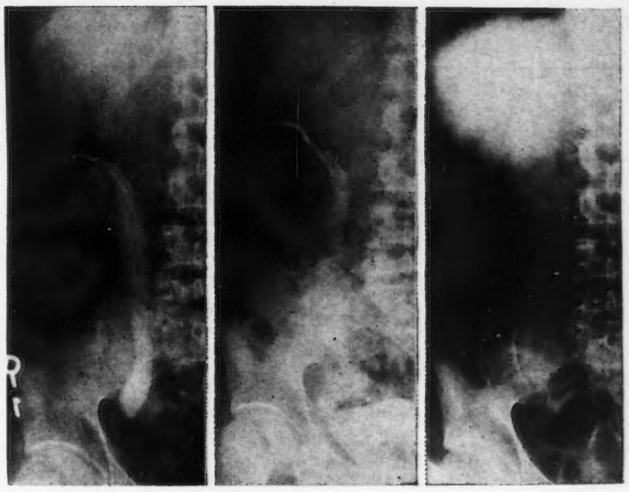

Fig. 1.—Pyelograms from Case 1. The film on the left was obtained by preoperative injection of nephrostomy tube, showing dilated ureter with complete obstruction at ureterovesical junction. The centre film shows postoperative injection of the nephrostomy tube with passage of dye across the ileal segment into the bladder. The film on the right is a postoperative intravenous pyelogram demonstrating improved filling of upper calyces.

Investigation showed the stricture and dilatation to be unchanged from previous examinations. Multiple small calculi were present in the dilated calyces. The NPN was normal. Urine contained numerous pus cells and cultured *P. pyocyanea* and *A. aerogenes.*

On March 7, 1958, after the acute inflammatory reaction had subsided, an ileocystoplasty was carried out, utilizing a 10-inch segment of terminal ileum. An end-to-end anastomosis was performed between the ileum and the dilated ureter at approximately the level of

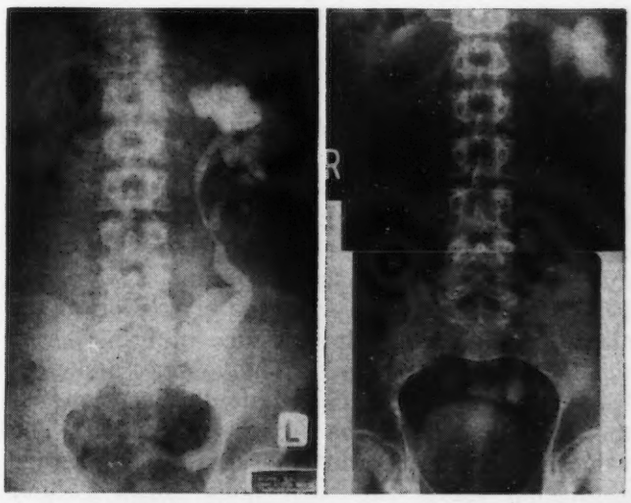

Fig. 2.—Intravenous pyelograms from Case 2. The film on the left taken preoperatively shows the dilated calyces and ureter with incomplete obstruction at the uretero-vesical junction. On the right, dye is seen to pass across the ileal segment to fill the bladder.

TABLE I.—RESULTS OF ANALYSIS OF URINE OBTAINED FROM NEPHROSTOMY AND BLADDER DRAINAGE SHOWING PERCENTAGE ABSORPTION OF ELECTROLYTES OCCURRING DURING PASSAGE ACROSS ILEAL SEGMENT

Date	*Fluid intake*	*Source*	*Urine volume*	*Specific gravity*	*Sodium mEq./l.*	*Potassium mEq./l.*	*Chloride mEq./l.*	*Sodium absorption*	*Potassium absorption*	*Chloride absorption*
Day 1	3405 c.c.	Kidney	1840	1.008	102.0	37.8	103.2	10%	31%	22%
		Bladder	620	1.004	91.8	26.0	80.5			
Day 2	3900 c.c.	Kidney	2340	1.006	98.6	25.8	110.0	14%	31%	42%
		Bladder	390	1.002	84.5	18.2	62.9			
Day 3	3600 c.c.	Kidney	2615	1.007	117.5	35.6	129.5	0	45%	28%
		Bladder	365	1.003	124.8	19.5	93.7			
Day 4	3840 c.c.	Kidney	2690	1.005	80.0	27.5	79.5	0.2%	47%	31%
		Bladder	340	1.001	88.0	16.4	61.9			
Day 5	3840 c.c.	Kidney	2690	1.008	120.0	32.7	114.0	0	0	13%
		Bladder	160	1.002	166.0	35.0	99.2			
Day 6	4440 c.c.	Kidney	2480	1.007	101.0	30.8	115.0	0	47%	26%
		Bladder	660	1.003	104.0	16.2	85.0			
Day 7	4140 c.c.	Kidney	3030	1.007	99.0	28.1	102.6	6%	49%	27%
		Bladder	970	1.003	93.0	14.3	74.4			
Day 8	4470 c.c.	Kidney	2380	1.007	83.0	28.1	96.3	0	22%	21%
		Bladder	1070	1.004	100.0	21.7	75.9			
Day 9	3750 c.c.	Kidney	1850	1.006	109.0	34.7	104.8	12%	19%	24%
		Bladder	1310	1.004	95.8	28.2	78.1			

the brim of the bony pelvis. The distal end of the loop was joined to the edges of a circular defect cut in the posterior aspect of the bladder fundus. Both anastomoses were extraperitonealized and the intervening bowel segment was tacked to the posterior wall of the pelvis.

The postoperative course was completely without incident. The patient was discharged from hospital on the 18th day, at which time he voided satisfactorily and was without complaints.

When reviewed after three months he was in good health but complained of a dull ache in the region of his left kidney at each voiding. The NPN level ranged from 54 to 58 mg. %. Serum electrolytes were normal. When on a large fluid intake he was able to void up to 500 c.c. and follow this in a few minutes with passage of a further 90 to 120 c.c. The patient was placed on a double voiding regimen, and his NPN level then returned to normal.

Intravenous pyelography showed improved function but no change in the degree of hydronephrosis (Fig. 2). Cystography revealed total reflux, with the voiding contraction followed by rapid emptying of the ileal segment as the bladder relaxed. A second voiding expelled a further 100 c.c., but a two-to-three-ounce residual persisted. The bladder neck was inspected and felt to be normal.

DISCUSSION

In Case 1, the rather unique situation of an isolated ileal segment to which access could be gained from either end was utilized for electrolyte studies. Removal of the urethral and nephrostomy catheters was deferred for a two-week period, during which 24-hour urine specimens were collected from each. This permitted estimation of the alterations occurring after passage of urine across the 12-inch bowel segment. The volumes and electrolyte values were corrected after calculations for the irrigation fluids had been subtracted. The values found are recorded in Table I. The average absorption values and their range for a 24-hour period are presented in Table II. During the period of this study, the patient was taking an ordinary hospital diet and a high intake of fluids. Daily urine output averaged 3000 c.c., more being drained by the nephrostomy tube than by the urethral catheter. Absorption of chloride was consistently greater than was that of sodium. On five occasions no absorption of sodium occurred. An interesting feature was the high absorption of potassium. Serum electrolytes remained normal during the study.

TABLE II.—RANGE AND AVERAGE OF ELECTROLYTE ABSORPTION DURING NINE 24-HOUR PERIODS PERCENTAGE ABSORPTION OF ELECTROLYTES

	Range	*Average*
Sodium	0—14%	4.6%
Potassium	0—49%	32.3%
Chloride	13—42%	26.0%

As mentioned in the case reports, both patients had total reflux. In the first case, this caused no symptoms. The second patient had renal pain on voiding. Active peristalsis has been demonstrated in these isolated segments of bowel and it would seem worth while, therefore, to fashion the anastomosis in an isoperistaltic manner, although this alone is not enough to prevent reflux. It is interesting that the first patient had a contracted bladder neck, presumably because of disuse over a nine-year period. It may be that the second patient would also benefit from a bladder neck resection in order to decrease the resistance to bladder emptying. It appeared that the amount of reflux occurring was directly related to the degree of bladder filling, and these patients have been advised to avoid overdistension by voiding at regular intervals. Double voiding has helped to reduce residual urine.

In the period since operation, there has been no significant change in the degree of dilatation. From the degree of chronic inflammation known to exist in these cases, it is likely that the hydronephrosis is fixed and will not alter greatly. Both patients are in excellent health, however, and have had no episodes of infection or other illness since operation.

SUMMARY AND CONCLUSIONS

Two examples of ileocystoplasty have been presented. Each patient possessed a solitary kidney with obstruction at the ureterovesical junction.

In one case the postoperative course was complicated by bladder neck obstruction requiring transurethral resection for its relief. Both patients have total ureteral reflux resulting in a residual urine. This has been reduced by instituting double-voiding.

Electrolyte absorption occurs in the bowel segment, but has caused no alteration in the serum values. This is likely due to the small absorptive surface involved and the fact that the ileum acts primarily as a conduit rather than a reservoir.

The early results in these two patients have been satisfactory and would suggest that the technique may be applicable to other cases having abnormalities at the ureterovesicular junction.

I wish to express my gratitude to Drs. C. Aberhart and C. Robson for their assistance and guidance in the management of these cases. This work was carried out at Sunnybrook Hospital (D.V.A.), Toronto, Ont.

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SURGICAL MANAGEMENT OF DIVERTICULITIS OF THE SIGMOID COLON*

S. E. O'BRIEN,† M.D., F.R.C.S.[C] and
K. I. MUSTARD, M.D., *Hamilton, Ont.*

RECENT EXPERIENCE with a small group of patients presenting serious complications of diverticulitis of the sigmoid colon has aroused our interest in the surgical management of this disease. Another stimulus to our interest has been the increasing reports in the literature advocating one-stage colon resection as the surgical procedure of choice.

In the past, the main indications for surgical treatment have been either the development of serious complications of diverticulitis or the inability of the clinician to exclude the possibility of carcinoma of the colon.

In recent years many authors have advocated a more radical approach and extended the indications for surgery to include those patients with severe or repeated bouts of uncomplicated diverticulitis which do not respond to conservative treatment. It is mainly in this latter group that one-stage sigmoid resection is becoming widely accepted as the treatment of choice.

It is our contention, however, that many patients present few or no symptoms until the sudden onset of a serious complication which demands surgical intervention. Certainly in these patients we still feel that staged procedures are the safest and best method of treatment. In many instances they present as problems which demand the utmost in surgical judgment to ensure their best and safest management.

*From the Surgical Services of the Hamilton General Hospital and St. Joseph's Hospital, Hamilton.
†Author's address: Suite 610, Medical Arts Bldg., Hamilton, Ont.

PATHOLOGY

An attack of diverticulitis may end in resolution or may go on to the development of certain complications. The diverticulum may perforate, producing generalized peritonitis of a fairly lethal type. More commonly, however, perforation will result in a localized abscess in the pericolic tissues. In the ideal situation, the abscess will rupture spontaneously into the lumen of the bowel and drain itself by that route. On the other hand it may enlarge, forming a tender palpable mass in the left lower quadrant or in the pelvis. Incision and drainage of such an abscess frequently results in a cutaneous fæcal fistula unless a proximal colostomy is made. If the abscess becomes adherent to an adjacent structure such as the bladder or a loop of small bowel, an internal fistula may result.

Repeated bouts of diverticulitis may produce extensive pericolic induration and fibrosis with stenosis of the lumen of the colon and large bowel obstruction. It is in these cases that differentiation from carcinoma is most difficult. Although barium enema examination reveals an obstruction, in diverticulitis the mucosal pattern is preserved and the involved segment of the colon is longer than in carcinoma. Furthermore, the appearance of diverticula in the adjacent colon lends support to the diagnosis of diverticulitis.

However, even with the abdomen open and the involved segment of bowel in the surgeon's hand, it is well known that differentiation from carcinoma may be impossible in as many as 25% of cases. Furthermore, one must appreciate that these two diseases are common and may co-exist in the same patient.

We do not, however, believe that there is any etiological relationship between diverticulitis and carcinoma.

ANALYSIS OF CASES

During the five-year period from 1952 to 1958, 64 patients underwent operative treatment for

diverticulitis of the sigmoid colon. We chose this period for analysis because during these years the most up-to-date antibiotic coverage and other supportive measures were available, and we felt that we would have a truer picture of the place of one-stage resection.

AGE AND SEX INCIDENCE

The average age in this series was 59.6 years. The youngest patient was 33 years and the oldest 86 years of age. Table I lists the number of cases in each decade. There were 29 males and 35 females. The usual reported incidence shows a definite preponderance of males over females—usually 2:1. In our series, the females held a slight edge.

TABLE I.—AGE INCIDENCE

Age groups (years)	*No. of cases*
30 - 39	3
40 - 49	9
50 - 59	17
60 - 69	20
70 - 79	14
80 - 89	1
	64

CLINICAL PICTURE

The signs and symptoms of diverticulitis are well known. Generally speaking, the disease presents with one of the following clinical pictures:

1. Recurring lower abdominal pain and constipation, with or without the development of a tender palpable mass in the left lower quadrant or in the pelvis.

2. Acute or chronic large bowel obstruction.

3. Acute localized or generalized peritonitis resulting from perforation. These patients are often acutely ill. Frequently they give no previous history suggestive of diverticulitis. Emergency operation is often necessary, frequently with an incorrect preoperative diagnosis such as acute appendicitis, ruptured ovarian cyst or some other acute abdominal condition. Critical judgment is needed in these cases to select the proper treatment. We feel that in most cases defunctioning transverse colostomy with drainage of the left lower abdomen is usually the treatment of choice. Closure of a perforation alone is rarely possible and frequently unsuccessful. Fæcal fistula will often follow such a procedure.

4. Urinary symptoms suggesting impending or actual vesico-colic fistula. Pneumaturia and the passage of fæcal urine are pathognomonic of fistula formation.

One of our patients with a vesico-colic fistula also presented with a right hydronephrosis due to ureteral obstruction by a large inflammatory mass in the sigmoid. Six months after transverse colostomy the hydronephrosis had completely disappeared and the sigmoid was easily resected with ureteral catheters in place.

Although Waugh and others have recommended one-stage resection in patients with vesico-colic fistula, we prefer a staged resection.

5. Rectal bleeding. This is not a common presenting symptom in diverticulitis, although it is reported in 8 to 20% of cases. When bleeding is a symptom, one should make every effort to rule out carcinoma, which is a much more likely source of hæmorrhage.

TABLE II.—INCIDENCE OF SYMPTOMS AND SIGNS

Symptoms and signs	*Cases*	*Per cent*
Abdominal pain	49	77%
Constipation	17	26%
Diarrhœa	10	16%
Bleeding	4	7%
Abdominal tenderness	32	50%
R. L. Q.	9	14%
L. L. Q.	18	28%
generalized	5	8%
Mass—abdominal	14	22%
pelvic	13	20%
Distension	6	9%
Urinary symptoms	9	14%
Pneumaturia	3	5%

Table II shows the incidence of the various signs and symptoms in this group of patients. Abdominal pain and tenderness are of course the most common symptoms. In nine (or 14%) tenderness was localized in the right lower quadrant, suggesting a diagnosis of acute appendicitis. In 42% of the patients a mass was palpable and in half of these patients the mass was palpable only on rectal or pelvic examination. Not infrequently, female patients with this disease are subjected to a laparotomy by a gynæcologist who has diagnosed an adnexal lesion.

Urinary symptoms occurred in nine patients, six of whom actually had a vesico-colic fistula. Only three of the patients with fistula experienced pneumaturia.

Of the four patients complaining of rectal bleeding, co-existing carcinoma was present in two.

PREOPERATIVE DIAGNOSIS

One of the most interesting features of this study was the high incidence of incorrect preoperative diagnosis, particularly in patients with acute complications.

Table III lists the various preoperative diagnoses recorded on the operation reports. Surprisingly enough, only 27 cases were correctly diagnosed preoperatively.

In those patients with acute complications such as perforation, an erroneous diagnosis of acute appendicitis is frequently made. This occurred in 10 or 15% of our patients. One would expect that an inflamed or perforated sigmoid loop which tended to lie over towards the right iliac fossa would be responsible for the confusing signs and symptoms. Moreover, when the presenting picture is that of generalized peritonitis of acute onset, the

TABLE III.—PREOPERATIVE DIAGNOSES

Preoperative diagnosis		*No. of cases*
Diverticulitis		27
(1) perforation	3	
(2) abscess	3	
(3) obstruction	4	
(4) fistula	6	
Acute appendicitis		10
Carcinoma		10
Intestinal obstruction		5
Ovarian tumour		4
Miscellaneous		4
No diagnosis		4
		64

appendix is usually considered first, being the commonest offender.

We have already mentioned the problem of distinguishing carcinoma from diverticulitis. In this series 10 or 15% of the patients were operated on with the preoperative diagnosis of carcinoma of the recto-sigmoid. In four of these patients, both diseases were subsequently found to be present.

Intestinal obstruction, without reference to cause, was diagnosed preoperatively in five patients. Three of these patients actually had small bowel obstruction due to adherence of a loop of ileum to the inflamed sigmoid.

Four patients were considered to have ovarian lesions because of the presence of a pelvic mass and the relative absence of bowel symptoms.

In the remaining patients, diverticulitis was an incidental finding at operation for some other condition, or else no specific preoperative diagnosis was recorded.

Table IV lists the actual pathological findings at operation.

TABLE IV.—FINDINGS AT OPERATION

Operative findings		*No. of cases*
Sigmoid mass		30
Abscess		11
Perforation		11
Fistula		7
Vesico-colic	6	
Entero-colic	1	
Obstruction		5
Co-existing carcinoma		4

TREATMENT

Until recent years surgical treatment was employed only when serious complications such as abscess, perforation, fistula or obstruction were present. Patients with uncomplicated diverticulitis were treated medically by rest, antibiotics, diet, and mild laxatives. When complications did occur, they were usually treated by defunctioning colostomy and drainage of abscesses. The colostomies were usually closed, without resection, after periods of six months to a year or more when the disease seemed quiescent. However, as Pemberton has pointed out, approximately two-thirds of these patients developed recurrence of their diverticulitis after closure of their colostomy.

It is now quite widely accepted that the patient who requires surgical treatment requires resection of the diseased segment of bowel, to ensure permanent relief of symptoms. The only important decision to be made is whether this resection should be carried out in one-stage or multiple stages. Certainly for the patient with a perforated colon or complete obstruction, a staged resection is much the safest procedure.

Preliminary colostomy is also advisable in cases with large abscesses or long-standing fistulas. Resection is certainly a much less hazardous procedure when carried out some months after colostomy. Usually considerable resolution of the inflammatory reaction has taken place in this interval, making resection much easier. Also when diverticulitis is found unexpectedly during laparotomy and the bowel has not been prepared, a staged procedure may be advisable.

We usually perform a right transverse colostomy with or without drainage of the left lower abdomen as indicated. Approximately six months later, resection of the sigmoid and anastomosis are carried out. The transverse colostomy is then closed as a third procedure.

Although this is a time-consuming and more expensive form of treatment, and carries a higher incidence of wound complications, we feel that, in the long run, it is much the safest course for these serious complications. If at the first operation we were unable to exclude the possibility of carcinoma, we would perform the resection much sooner—say in four to six weeks.

The one technical difficulty we have encountered is due to the narrow lumen of the defunctioned sigmoid, which makes the anastomosis a little more difficult. This is more than offset, however, by the relative absence of œdema, induration and dense adhesions.

Occasionally, an inflamed or perforated loop of sigmoid can be exteriorized initially as a Mikulicz procedure, leaving a double-barrelled sigmoid colostomy which is closed at a second stage. In our experience, this is not often possible because of the low level of the lesion, the extent of the inflammatory reaction and the thickening and shortening of the mesocolon. Furthermore, it is not a good operation if one cannot exclude the possibility of cancer.

More recently, many authors are advocating the more widespread application of one-stage sigmoid resection in diverticulitis. We think that one should be most careful in the selection of patients for this procedure. Allen, Donaldson and Welch lay down the following criteria for one-stage resection:

1. Good general condition and a relatively young patient.

2. Absence of complications such as obstruction, perforation or fistula.

3. A well-prepared colon.

They consider that many patients with repeated bouts of uncomplicated diverticulitis, or with early

TABLE V.—OPERATIVE PROCEDURES

Operative procedure	*No. of cases*
3-stage resection	18
1-stage resection	10
2-stage resection	2
Colostomy (with or without drainage of abscess)	14
Mikulicz resection	6
Laparotomy	8
Appendectomy and drainage	3
Abdomino-perineal	2
Hartman resection	1
	64

urinary symptoms suggesting impending fistula, fall into this group. While this is undoubtedly true, the majority of our patients have presented for surgical treatment with relatively serious complications and could not be placed in this category. We would hope that in future, with better education of physicians, more patients will be referred for surgical treatment earlier in the course of their disease before complications have developed. Only in this way will one-stage resection become a more popular operation in diverticulitis.

Table V shows the various operative procedures carried out in this group of patients. The wide variety of operations performed indicates that no one procedure is applicable to all cases.

As might be expected, three-stage resection was the commonest procedure, having been carried out in 18 cases. In 14 cases surgical treatment was limited to a proximal colostomy and in only one of these patients was the colostomy subsequently closed. Three of these patients died postoperatively and two were found to have inoperable carcinoma in addition to diverticulitis. The remaining patients either were too elderly or had some systemic disease which prevented resection, and apparently were left with a permanent colostomy.

One-stage resection was carried out in ten cases, and in six cases an exteriorization procedure was possible. Three patients who were operated on for acute appendicitis and found to have acute diverticulitis, underwent appendectomy alone and made an uneventful recovery.

Two of the patients who had a preoperative diagnosis of carcinoma of the recto-sigmoid were subjected to abdomino-perineal resection because of a misleading radiological picture. In neither case was a biopsy obtained, and only one of them underwent sigmoidoscopy preoperatively. We feel that sigmoidoscopic examination and biopsy are essential features of the investigation of patients with diverticulitis, particularly when carcinoma is suspected.

RESULTS

There were six postoperative deaths in this series, giving a mortality rate of 9.5%. The cause of death was known in five of these cases; one patient died of peritonitis, one of cardiac failure, one of hepatic failure, one of bronchogenic carcinoma and one of mesenteric thrombosis. Three of the deaths occurred after transverse colostomy in patients who were acutely ill with perforation or obstruction. One elderly man died of cardiac failure after a laparotomy for appendicitis at which acute uncomplicated diverticulitis was found but only appendectomy was performed. One patient died after a one-stage resection, but the cause of death was never determined.

The remaining death occurred in a rather unusual case. A 57-year-old man had a perforation and generalized peritonitis which was treated by transverse colostomy and drainage. Six months later he returned for a sigmoid resection. On his second postoperative day he was found to have atelectasis of the left lung. Bronchoscopy revealed a tumour in the left main bronchus which was reported on biopsy to be a bronchogenic carcinoma. Two weeks after the sigmoid resection, he underwent left pneumonectomy and died very suddenly six days after this operation. An autopsy was not performed, but death was ascribed to either coronary occlusion or pulmonary embolism.

TABLE VI.—POSTOPERATIVE COMPLICATIONS

Wound infection	9*
Fæcal fistula	3
Pelvic abscess	2
Postoperative hæmorrhage	2
Intestinal obstruction	1
Paralytic ileus	1
Osteomyelitis of pubis	1
Furunculosis of buttocks	1

*(2 one-stage resections)

The postoperative complications are listed in Table VI. As might be expected, wound infection was the commonest complication, occurring in nine cases. Only two of these infections followed one-stage resection. Fæcal fistula occurred in three patients, one of whom required subsequent operative closure. None of the fistulas occurred after one-stage resection.

The patient with intestinal obstruction had a Mikulicz procedure performed for perforated diverticulitis. After closure of the colostomy she developed intermittent small bowel obstruction. This was subsequently proved to be due to Crohn's disease of the terminal ileum, and she was subjected to a two-stage right hemicolectomy. The case of osteomyelitis of the pubis followed the third stage of a three-stage resection for vesico-colic fistula and required a sequestrectomy.

CONCLUSIONS

We have presented a series of 64 patients undergoing surgical treatment for diverticulitis of the sigmoid colon during a recent five-year period. The majority of these patients were operated upon for complications of their disease. Frequently, these complications were of acute onset with few or no previous symptoms of diverticulitis. The diagnosis

was often missed preoperatively and the abdomen entered with some other diagnosis in mind. Under these circumstances we have felt that a proximal colostomy followed by a staged resection is the treatment of choice.

On the other hand, there are a group of patients with repeated bouts of uncomplicated diverticulitis, or with very early and minimal complications, in whom a more radical approach is recommended. In these cases, one-stage sigmoid resection may be performed without added risk, and with much shorter periods in hospital and considerably less expense. It is to be hoped that in the future more patients in this latter category will be referred for surgical treatment before the onset of serious complications.

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RÉSUMÉ

Au cours d'une période de cinq ans la majorité d'une série de 64 malades ayant passé par la chirurgie pour le traitement de diverticulite du sigmoïde ont été opérés pour des complications de leur maladie. Dans plusieurs cas ces complications ont débuté brusquement avec peu ou pas d'antécédents symptomatologiques de diverticulite. Le diagnostic préopératoire fut souvent erroné, et l'opération entreprise avec une autre impression diagnostique en vue. Dans ces circonstances les auteurs prétendent que le meilleur traitement consiste en une colostomie proximale suivie d'une résection par stages. D'autre part il existe un groupe de malades accusant des attaques répétées de diverticulite avec des complications peu nombreuses ou très légères chez qui on peut se permettre une intervention plus directe. Dans ces cas une résection du sigmoïde en un stage peut être pratiquée sans augmenter les risques, tout en diminuant la durée et les frais d'hospitalisation. Souhaitons qu'à l'avenir un plus grand nombre de malades dans cette catégorie soient opérés avant l'installation de complications sérieuses.

FARMER'S LUNG OR BRONCHOMYCOSIS FENISECARUM*

J. J. QUINLAN, M.D. and J. E. HILTZ, M.D.,
Kentville, N.S.

THE TERM farmer's lung or *bronchomycosis fenisecarum* (fenisecarum: haymakers') has been applied to an occupational disease occurring chiefly among hay and grain workers and stable or cattle men. A similar condition has also been described among other workers handling mouldy materials such as those used in the manufacture of textiles.

Farmer's lung was first described by Campbell,[1] who recorded five cases, and the condition was fully reviewed in a later publication by Fawcitt[2] in 1938. Unlike most fungus diseases, invasion of the lung tissue by the infective agent does not appear to occur. Indeed, it has been called a "mould spore pneumonoconiosis" by one author. It has been suggested that the symptoms are due initially to hypersensitivity to spores. This hypersensitivity may cause a condition simulating asthma or chronic bronchitis and even bronchopneumonia or interstitial pneumonitis in the later stages. At times, patients have been referred to tuberculosis institutions because they were suspected of having miliary tuberculosis. At the Nova Scotia Sanatorium, our attention was first focused on this problem when a patient was referred to us with a mistaken diagnosis of miliary tuberculosis but giving a history of having opened a silo several weeks previously. Such silos are usually covered by a thick layer of mould which must be broken up and removed during the opening process.

One of the clinical features of farmer's lung is its seasonal nature. Its onset is usually acute and patients may be quite ill with severe dyspnœa but usually without bronchospasm. Fever is not high but the blood sedimentation rate may be increased. There is frequently marked cough but very scanty sputum, which is usually frothy. Exacerbations occur on further contact with the source of the causative organisms. Rarely does the disease progress to the development of cyanosis or emaciation but these can occur and the outcome can be fatal.

The radiological picture varies considerably. As mentioned already, the appearances may be the same as those of miliary tuberculosis or other diseases causing disseminated fine nodular or fibrous shadows in both lungs. The apices of the lungs are least involved. The density of the mottling may gradually increase. In some cases there may be patchy clouding which later becomes dense and confluent, simulating pneumonia or bronchopneumonia. The hilar shadows may be enlarged. The roentgenological picture may on occasion be very similar to that of tuberculosis or sarcoidosis.

The diagnosis is usually quite difficult to make. One has to depend to a large extent upon the occupational history and the acute onset of symptoms combined with the radiological picture. So-called "farmer's lung" should be suspected in people who have been in contact with a recently

*From the Nova Scotia Sanatorium, Kentville, N.S.

opened silo or mouldy wet hay, and who present with rather severe dyspnœa, fever and a chest film which is definitely abnormal, usually without gross consolidation present.

Bacteriologically, a number of fungi have been incriminated, frequently as spores or conidia but sometimes in the mycelium stage. These include *Histoplasma capsulatum, Aspergillus, Monilia, Penicillium, Coccidioides* and *Mucor.* A personal communication[3] from the Laboratory of Plant Pathology in Kentville indicated that the following fungi were found in mouldy grass ensilage examined there: *Aspergillus, Mucor, Pullularia, Penicillium, Spicaria* and *Actinomyces.*

It is interesting to note that the spores of microfungi which infect man are mainly 3 to 5 μ in diameter. It has been established that the size of particles of silica which are harmful to the lungs and cause the development of silicosis varies from 2 to 5 μ. These particles can penetrate right to the bronchioles and air sacs, whereas larger particles are trapped and removed by the protective mechanism of the breathing passages such as the cilia of the epithelium. There may be some justification for the name mould-spore pneumonoconiosis.

The clinical signs are those of bronchitis or asthma. The essential feature is the marked shortness of breath. Duncan[4] suggests that "broken wind" of horses, a disorder similar to farmer's lung in its symptomatology, is caused by feeding on mouldy hay and it can be prevented if the hay is wetted sufficiently to prevent the dust from rising and being inhaled.

The prognosis is generally good in this disease. It is rarely fatal. Once removed from the exciting factor of the mould spores, the patient rapidly improves, although relapses occur readily with renewed exposure. Drug therapy has little effect on the disease although potassium iodide has been used in the treatment of the very distressing cough. Antihistamine drugs have caused improvement in some cases. The antibiotics are of no value except when there is superimposed bacterial infection.

CASE 1.—Our attention was first focused on farmer's lung with the admission of a patient, R.J.S., aged 30, in December 1951. Before coming to the Sanatorium, this man's illness had been tentatively diagnosed as miliary tuberculosis. He was a farmer and had enjoyed good health until a month before admission. At that time he noticed some shortness of breath. This was followed by an acute respiratory illness with cough, sputum, dyspnœa and fever to 102° F. He rapidly improved on therapy with sulfonamides although his cough persisted. However, after he went back to work about the farm, his symptoms returned with fever, shortness of breath, tiredness and weakness. He was then admitted to a nearby hospital, where radiographic appearances were those of a disseminated inflammatory lesion throughout both lungs. Upon subsequent admission to the Sanatorium he was fully investigated. Specimens of sputum were positive for a mixed bacterial flora and *Mucor.* The tuberculin test was negative. Bronchoscopy revealed the production of profuse watery secretion from both lungs, but biopsy of the supraclavicular fat pad failed to reveal evidence of any pathological process. This was classified as a case of farmer's lung, as on further questioning the patient stated that his trouble began when he opened up his silo in the fall of 1951. He said that there was mould on top of the ensilage and the "fumes" bothered him greatly. Every day that he worked in it he felt worse. At the Sanatorium his symptoms rapidly regressed and by August 1952 his chest film was normal. After his return home from the Sanatorium in three months' time, contact with ensilage again precipitated an attack. When this was repeated, he sold the farm.

Our findings in this case led us to look back over some of our previous patients who were investigated at the Sanatorium and discharged undiagnosed or incompletely diagnosed. Among these were some farmers.

CASE 2.—J.A.M., aged 44, was admitted to the Sanatorium on January 4, 1937. He gave a history of having developed a very severe cough and dyspnœa which he believed was due to chaff encountered while threshing oats, and also to sawdust from his mill. He was hospitalized for a short time and while in hospital felt much improved but once he returned to his work the symptoms reappeared. His cough persisted, and on radiological examination changes were noted in the right lung. He was admitted to the Sanatorium for investigation and on further questioning it was found that his symptoms occurred after threshing. Here again improvement was rapid once the patient was removed from contact with the grain and its probable contaminating spores. Our last follow-up examination three months later revealed normal lung findings with no symptoms.

CASE 3.—G.A.J. This 30-year-old man's illness began as an acute upper lobe pneumonia on the left side. Radiological examination revealed scattered nodular lesions throughout both lung fields with consolidation in the left upper lobe. His occupation was farming and he gave a history of having worked in a newly opened silo and also cleaning out hen pits. He was not acutely ill. Before admission, the diagnosis was that of miliary tuberculosis; on treatment he made slow but steady improvement and by June his lung fields were completely clear. His tuberculin test was negative. His sputum yielded yeast and Gram-negative rods. Other tests for diseases causing disseminated lesions in both lungs were negative and it was felt that this man's illness represented a "farmer's lung". He has remained well to date.

CASE 4.—W.K., male, aged 47, was referred to us in March 1952 for consultation about the radiological appearance of his lung fields. The patient had developed shortness of breath before Christmas. On January 16, 1952, he began running a fever and was ordered to bed. Diagnosis was "influenza". In five days his temperature was normal but shortness of breath persisted. Eight days later, while working in "musty straw", he had an attack of paroxysmal coughing. His temperature reached 103° F. He received sulfonamides

and aureomycin (chlortetracycline HCl) without much improvement and was admitted to hospital, where administration of terramycin brought improvement. During this time his only symptom was dyspnœa with little cough and no expectoration.

This patient had never cleaned a silo but he attributed his illness to the fact that he had worked with damp straw, covered with a greenish white mould. This statement was checked by the Divisional Medical Health Officer, who verified its accuracy.

By March the patient felt perfectly well. His chest films of February 8 and 23 showed a typical picture of "farmer's lung" with improvement in the latter film. Unfortunately, additional follow-up radiographs were not available to us.

CASE 5.—R.E.P., a 38-year-old farmer, was admitted to the Sanatorium in March 1957. He gave a history of having had general malaise, shortness of breath, fever, cough and sputum for some time. On admission to the Sanatorium investigation revealed a fine nodular lesion in both lungs. Complete investigation failed to reveal any evidence of the presence of the usual causes of bilateral nodular lesions. Tuberculin tests and histoplasmin tests were negative in all strengths. On close questioning this man gave a history of working with mouldy hay outdoors; on the evening of the same day he had come down with chills and fever. The hay was very dusty. He rapidly improved without any specific treatment and on discharge there was considerable improvement in his lung lesion. Fungi were not demonstrated in the sputum but clinically this was considered to be a case of bronchomycosis.

SUMMARY

The entity of so-called "farmer's lung" has been reviewed. It would appear to be a significant condition in areas such as the Annapolis Valley of Nova Scotia, where so many people are farmers, raising cattle and occupied with ensilage and sometimes with mouldy hay or the threshing of grain. It is suggested that the disease is primarily a phenomenon due to fungus spores which exist in wet hay or grain and on the top of matured ensilage. Some acute pulmonary illnesses which occur in farmers may on occasion be due to a mould spore pneumonoconiosis or "farmer's lung".

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RÉSUMÉ

Il existe dans la vallée d'Annapolis une entité morbide connue vulgairement sous le nom de *poumon de fermier* et qui semble atteindre surtout les éleveurs de bétail et plus particulièrement les ensileurs qui manipulent du fourrage fermenté ou du foin moisi, ou qui s'occupent du battage du grain. La symptomatologie comporte de la dyspnée souvent d'un début brusque, des spasmes bronchiques, de la fièvre, une toux tenace, de rares expectorations spumeuses et un taux de sédimentation élevée. Ces manifestations d'ordre allergique, rarement fatales, semblent causées par une hypersensibilité à des spores de champignon qui se retrouvent dans le foin ou le grain humide ou sur l'ensilage avancé. Les auteurs sont d'avis que certaines pneumoconioses aiguës des cultivateurs peuvent quelquefois être causées par des spores de moisissure comme cela semble être le cas dans le *poumon de fermier*.

THE T.P.I. TEST IN RELATION TO THE STANDARD TESTS FOR SYPHILIS*

C. L. HUNT, M.D., *Vancouver, B.C.*

THE SEROLOGICAL TESTS usually employed as screening tests in the detection of syphilis—the V.D.R.L. and complement fixation tests—depend upon the presence of non-specific antibodies or reagins. Unfortunately, many non-spirochætal conditions can cause these tests to become positive—but usually only for a short while.

The treponema pallidum immobilization (T.P.I.) test, on the other hand, depends upon the presence in the serum of a *specific* antibody to the spirochæte, which when incubated with living spirochætes will destroy them.

The standard serological tests for syphilis—the V.D.R.L. and complement fixation—usually become positive about four to six weeks after infection. The T.P.I. test, on the other hand, does not usually become positive until six to ten weeks after infection.

It is, therefore, possible in the early stages of a syphilitic infection to find the standard serological tests positive and the T.P.I. test negative. If treatment is commenced during this stage, and the patient cured of his infection, the T.P.I. test may never become positive. If, however, a patient is treated late in his infection, the standard tests usually show a gradual decline in titre, ultimately becoming negative or nearly so, while the T.P.I. test continues to remain positive for many more years, though it too may ultimately become negative. *This situation may arise also without the patient's ever having had any treatment.*

These facts explain why some patients may have very weak positive or doubtful standard tests and yet show a positive T.P.I. test.

From these remarks it will be seen that the T.P.I. test is useful in determining whether or not a person has ever had syphilis (provided he was not cured in the very early stages), but does not indicate the present state of the infection or the adequacy of the patient's past treatment. There are, therefore, very definite limitations in its usefulness.

*From the Division of Venereal Disease Control, Department of Health and Welfare, 828 West 10th Avenue, Vancouver 9.

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TABLE I.—THE T.P.I. TEST IN PATIENTS WITH A DOUBTFUL OR POSITIVE V.D.R.L. AND NEGATIVE COMPLEMENT FIXATION

		Number of cases			*T.P.I. positive*			*T.P.I. negative*		
V.D.R.L.	*C.F.*	*M.*	*F.*	*Total*	*M.*	*F.*	*Total*	*M.*	*F.*	*Total*
D	—	53	50	103	29 (55%)	17 (34%)	46 (44.7%)	24 (45%)	33 (66%)	57 (55.3%)
+ 1/1	—	25	27	52	11 (44%)	7 (26%)	18 (34.6%)	14 (56%)	20 (74%)	34 (65.4%)
+ 1/2	—	12	25	37	5 (41.7%)	6 (24%)	11 (30%)	7 (58.3%)	19 (76%)	26 (70%)
+ 1/4	—	3	8	11	1 (33%)	1 (12.5%)	2 (18%)	2 (67%)	7 (87.5%)	9 (82%)
+ 1/8	—	4	4	8	1 (25%)	—	1 (12.5%)	3 (75%)	4 (100%)	7 (88.5%)
Total.....		97	114	211	47 (48.4%)	31 (27.2%)	78 (37%)	50 (51.6%)	83 (72.8%)	133 (63%)

The T.P.I. test is more costly and time-consuming than the standard screening tests usually employed. For this reason, it is a local requirement that every effort must first have been made to arrive at a diagnosis without resorting to the T.P.I. test.

If the history indicates that the patient has had syphilis, or has been treated for it, the T.P.I. test can give us no added useful information. In the absence of a positive history or clinical findings, the standard blood test should always be repeated, preferably at least two weeks after the first positive test, to make sure that the titre has not decreased significantly or become negative in the meantime or that it does not show characteristics suggestive of a false positive reaction.

A physical examination should be done to exclude, as far as possible, the presence of conditions known to cause frequent biological false positive reactions. If such conditions exist, or the serological findings are such as to suggest a possible false positive reaction, it is better to wait two or three weeks and repeat the serological test. The information thus provided may obviate the need for a T.P.I. test.

EXPERIENCE IN B.C.

This preamble is given in order to show the types of cases in which T.P.I. tests have been done in British Columbia over the past few years. With this in mind, the 462 cases (219 in women and 243 in men) in which T.P.I. tests were done in 1957 and early 1958 may be of interest. In many instances, the numbers are too small to be of statistical significance, but the trends indicated have proved by subsequent experience to be fairly accurate and have formed a useful working guide.

Approximately one-third of all those having a persistently doubtful or positive V.D.R.L. and negative complement fixation were T.P.I. positive (37% of 211 cases). That means that almost two-thirds of these cases were probably false positive reactors (see Table I).

A further analysis of this group gives the following interesting information. Only 55% of those having a *doubtful* V.D.R.L. and negative complement fixation were T.P.I. negative. On the other hand, as the titre of the V.D.R.L. rose (the complement fixation remaining negative), the tendency for it to be a false positive reaction also rose. Those with a V.D.R.L. positive 1:8 and a negative complement fixation were almost all T.P.I. negative.

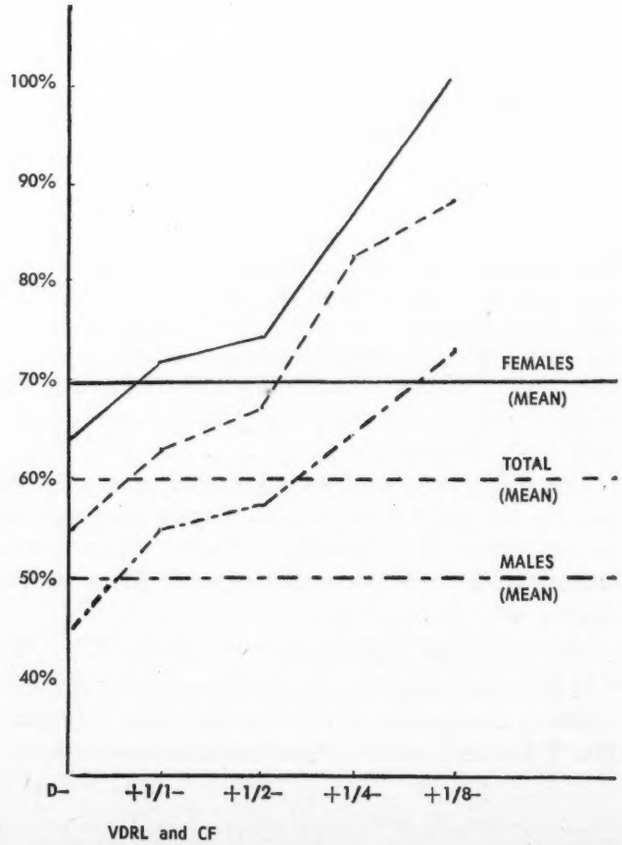

Fig. 1

TABLE II.—THE T.P.I. TEST IN RELATION TO THE STANDARD SEROLOGICAL TESTS

V.D.R.L.	*C.F.*	*T.P.I. positive*	*T.P.I. negative*	*Total cases*	*Remarks*
Doubtful	—	3	13	16	All but one of these were old treated cases with residual C.V.S. or C.N.S. changes.
Negative	D or +	7	9	16	—
Doubtful or positive	—	78 (37%)	133 (63%)	211	97 M.—48.4% positive 114 F. —27.2% positive
Doubtful or positive	+	184 (84%)	35 (16%)	219	124 M.— 92% positive 95 F. —73.7% positive
Total		272 (59.0%)	190 (41.0%)	462	243 M.—69.5% positive 219 F. —47% positive

When the sexes were considered separately, of those showing a doubtful V.D.R.L. and negative complement fixation, only 45% of the men were T.P.I. negative, whereas 66% of the women were apparently false positive reactors.

As the titre of the V.D.R.L. rose, the men showed a slight increase in the proportion of false positive reactors, whereas the incidence of false positive reactors among the women continued to rise steeply with the rise in V.D.R.L. titre (see Fig. 1).

In summarizing this group: males with a negative complement fixation and a doubtful V.D.R.L. had only a 45% chance of being false positive reactors. Women with these same findings appeared to have a 66% chance of being false positive reactors, the percentage rising steeply with the rise in V.D.R.L. titre. A very small number in this series (two or three cases) were actually cases of early syphilis in which the T.P.I. test had not yet become positive. Hence the recommendation that two or three weeks be allowed to elapse between consecutive standard tests, before performance of the T.P.I. test.

In 219 cases both standard tests were positive. Of these only thirty-five (16%) were false positive reactors or T.P.I. negative (see Table II).

Of these 35 patients, 25 were women and only 10 men, a proportion of 5:2.

In all the males with an apparent false positive reaction, the V.D.R.L. was doubtful, or positive only in a dilution of 1:1. In the women, the positive dilutions tended to be higher, 21 of the 25 having a titre of 1:2 or higher.

In 16 cases both standard tests were negative. Three were T.P.I. positive. Each of these was an old, fully treated case—two of tabes and one of general paresis. The remaining 13 were T.P.I. negative. However, all but one of these patients had many years previously been treated for syphilis and had signs of residual syphilitic damage. It was as a result of the positive clinical findings that the T.P.I. tests were carried out on these cases. Obviously, the T.P.I. gave little useful information in these instances.

This further illustrates the limitations in the usefulness of the T.P.I. test and shows that when the patient has been fully treated and the standard tests have become negative, the T.P.I. test may also ultimately revert to negative.

In 16 cases the V.D.R.L. test was negative and complement fixation doubtful or positive. Of these, nine were T.P.I. positive and seven were T.P.I. negative. Some of those with a positive T.P.I. test had a negative V.D.R.L. in the first test and a positive in the second or third test. These were possibly cases of early syphilis in which the blood was becoming positive.

CONCLUSIONS

These investigations would appear to support the view that the T.P.I. test has a very definite place in determining when a persistently positive standard test is due to syphilis, in the absence of any other positive findings.

A negative T.P.I. test does not rule out syphilis in the very early stages, or in the late stages when the standard tests have become negative. A positive T.P.I. test does not indicate the present stage of an infection, but merely that a patient has at some time been infected. In this respect, it is no more informative than a positive Schick test or a positive tuberculin test. False positive tests may be recorded in those having antibiotics circulating in the blood stream.

These investigations have also shed some light on the occurrence of biological false positive reactors to the standard serological tests. Approximately 16% of all cases with a positive V.D.R.L. test and positive complement fixation are presumably not suffering from syphilis. In those with a doubtful or positive V.D.R.L. and a negative complement fixation test, approximately 52% of men and 73% of women are likely to be false positive reactors. The percentage of false positive reactors in this group rises steeply with increases in the V.D.R.L. titre.

In all instances, women appear to have a higher proportion of biological false positive reactions than men.

RÉSUMÉ

Les recherches dont on fait part dans cet article semblent indiquer que le test d'immobilisation tréponémique possède une importance réelle dans l'identification de la syphilis comme cause d'épreuves sérologiques constamment positives en l'absence d'autres signes positifs. Une épreuve

de Nelson et Mayer négative n'élimine pas la syphilis à ses stages les plus précoces ou les plus tardifs quand les épreuves sérologiques habituelles sont devenues négatives. Un résultat positif par contre n'offre aucune indication du stage qu'a atteint l'infection mais montre seulement que le malade a été infecté à une période antérieure quelconque. A cet égard il n'offre pas plus de renseignement qu'une épreuve de Schick ou une cuti-réaction positives. Un faux positif peut être obtenu chez ceux dont le sang circulant contient des antibiotiques.

Ces recherches ont également jeté quelques lumières sur le problème des résultats faussement positifs dans les épreuves sérologiques régulières. Environ 16% de tous les cas rapportés positifs d'après les épreuves sérologiques de dépistage et de dérivation du complément ne sont pas des syphilitiques. Dans les test de résultat douteux ou positif et lorsque la fixation du complément est négative, environ 52% des hommes et 73% des femmes peuvent donner une immobilisation tréponémique faussement positive. Le pourcentage des faux positifs de ce groupe augmente rapidement avec toute élévation du titre dans les épreuves sérologiques. Les femmes semblent toujours donner une plus grande proportion de résultats biologiques faussement positifs que les hommes.

METABOLIC STUDIES IN ATHEROSCLEROSIS*

I. METABOLIC PATHWAY OF C^{14}-LABELLED ALPHA-TOCOPHEROL

JOSEPH STERNBERG, M.D.† and
ENID PASCOE-DAWSON, Ph.D.,‡
Montreal

IN THE FIELD of atherosclerotic disease, the practitioner is faced with a bewildering array of therapies as well as physiopathological theories. The reason for this confusing situation is that, until now, no theory has offered a satisfactory explanation for the multiple facets of human atherosclerosis. This is reflected in the numerous therapies, each having its own advocates, but none being so simple and satisfactory as the indisputable triumph of vaccination.

In diagnosis, serum cholesterol determination can be complemented to a certain extent by examination of the lipoprotein pattern, but neither of these tests offers a diagnostic or prognostic certitude, nor can any other test as yet. Although supported with the same enthusiasm by their promoters, some of the therapies offered to the physician are even conflicting, such as the suppression of thyroid function by radioiodine and the cholesterol-lowering treatments. The former therapy, supported and applied by Blumgart,[1] is based upon the assumption that induced thyroid hypofunction will reduce the circulation load and thus diminish the strain imposed upon the deficient myocardium. Yet, it is a well-known fact that thyroid hypofunction is accompanied by a significant increase in serum cholesterol and increase of the β/α lipoprotein ratio; even the sustainers of radioiodine therapy do not venture to deny completely this serious disadvantage.

Partisans of the dietary approach have a "biochemical objective", namely to reduce a high serum cholesterol level or a high lipoprotein β/α ratio to the supposedly normal or ideal values; however, it has not been ascertained that the lowering of serum cholesterol level of lipoprotein ratio is always effective in atherosclerotic disease. The clinician gives anticoagulants and vasodilators when immediate relief of symptoms is sought, and in emergencies seldom takes into consideration other criteria; a cautious practitioner will give a multi-facet therapy without knowing which case might benefit most from one or other of these procedures.

The unifying link between these various concepts and attitudes has yet to be found. It is the objective of the Clinical Research Department of the Montreal Institute of Cardiology to offer a physiological background to some of these concepts and to reduce the various therapeutic attitudes to a common denominator. It seems logical that the common denominator should be the serum lipoprotein level and the mechanism regulating the metabolism of their components. Better understanding of these mechanisms might lead to more effective application of therapy.

The following studies will be presented: (1) radioiodine studies in human atherosclerosis; (2) action of high-fat and cholesterol-rich diets upon thyroid function in experimental animals; (3) studies on the mechanism of lipoprotein-lowering action of œstrogens, and (4) metabolic studies with radioactive α-tocopherol.

The last study is the object of the present paper.

FUNCTIONS AND CLINICAL USE OF VITAMIN E: PRESENT KNOWLEDGE

This intriguing vitamin has been the subject of many discussions, sometimes lacking in scientific objectivity, and alternately has been heralded as a panacea or minimized by its adversaries as an almost valueless metabolite. It has been empirically used for years in the treatment of threatened abortion,[2] menopausal disturbances,[3] muscular dystrophy[4] and cardiovascular diseases.[5, 6] Supporters of the use of α-tocopherol in heart disease claim

*The work presented in this paper has been the object of communications at the annual meeting of the Canadian Physiological Society, Kingston, Ont., June 1958, the annual meeting of the Society of Nuclear Medicine, Los Angeles, June 1958, and the 4th International Congress of Biochemistry, Vienna, September 1958.
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†Head, Clinical Research Department, Montreal Institute of Cardiology; Head, Radioisotope Unit, Institute of Microbiology and Hygiene, University of Montreal.
‡Research Assistant, Clinical Research Department, Montreal Institute of Cardiology.

that its effects are due to the "oxygen sparing action" exerted by this vitamin *in vivo*. Thus, an increased tissue level of α-tocopherol might allow the myocardium to perform its work while consuming less oxygen than that required by a normal muscle. Yet, clinical trials are unsatisfactory because of lack of basic studies; even the role of the oxygen-sparing action of α-tocopherol is being questioned as the most important factor in its therapeutic use. Nason and associates[7] contend that the antioxidant role of vitamin E is only secondary to other actions: indeed, a significant relationship was established between α-tocopherol and the cytochrome respiratory chain. According to these authors, α-tocopherol is a co-factor of cytochrome-C reductase. A delipidated extract of heart muscle, the richest tissue in this enzyme, is devoid of the specific action of cytochrome-C reductase; the enzyme activity is quantitatively restored by addition of α-tocopherol. Other enzyme cycles are being investigated, especially the high energy phosphorylation chain, where it seems that α-tocopherol might play a role; however, the results are not so spectacular as in the case of cytochrome-C reductase.[8, 9] The antioxidant action of α-tocopherol has experienced a revival of interest since the popularization of diets with a high content of unsaturated fatty acids; indeed, the protective action exerted by vitamin E against irreversible oxidation of unsaturated fatty acids is well known.[10] Finally, the diminished red cell resistance to hæmolysis in vitamin E deficient animals seems to have aroused the interest of pædiatricians, who seek a similar etiology in some hæmolytic anæmias in infancy.[11] Physical fitness and increased resistance to physical stress have been achieved with massive doses of α-tocopherol in animals and even in human athletes,[12] and enthusiastic supporters claim that it brings a sense of well-being to the user.

These interesting though disparate facts show that a reappraisal of our knowledge of the metabolism of α-tocopherol is necessary, if rational therapy is to be recommended. One of the most difficult problems in therapy is the great divergence in dosage recommended: some authors favour small to moderate doses in the range of 50-100 mg. a day, whereas others state that no significant effect can be obtained with doses lower than 1000-2000 mg. a day, sometimes even 40,000 mg. a day![13] A serious criticism of the use of high doses of the vitamin is our ignorance of their fate, which might differ from that of doses of α-tocopherol corresponding to the daily requirements of the body. At the former level, the vitamin might act as a drug, with perhaps only a remote relationship to its physiological role. The occurrence of chemical and clinical symptoms of hypervitaminosis D and A suggests that the clinician should be aware of a similar possibility in the case of vitamin E overdosage. A paper by Prosperi and Borselli[14] mentions degenerative changes in liver, myocardium and brain, in guinea pigs treated with 600-1200 mg. daily. However, no clinically detectable signs have been noted by those who use high doses in treatment or even as an adjuvant in healthy persons, though this does not preclude the need for an objective estimate of the correct dosage in man.

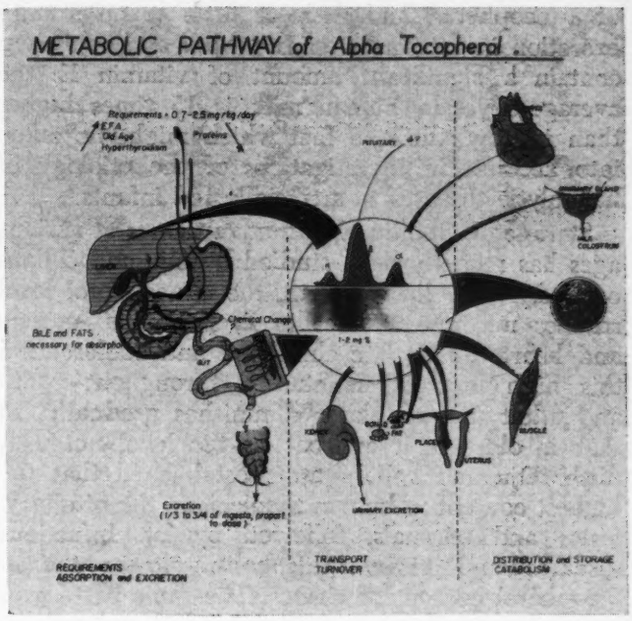

Fig. 1.—Metabolic pathway of α-tocopherol. Diagram based upon data obtained with stable α-tocopherol.

Our knowledge of the metabolic pathway of α-tocopherol is illustrated in Fig. 1, compiled from data in recent literature.

The daily requirements for experimental animals are estimated at between 0.7 and 2.5 mg./kg. body weight, and vary greatly with the diet. As previously mentioned, essential fatty acids increase the need for vitamin E, while a high protein diet diminishes the requirement. Old age and hyperthyroidism both increase vitamin E requirement.[15] In man, Bicknell and Prescott[16] established the minimum daily requirement at not below 5 mg.; these authors strongly maintain that vitamin E is essential for man, even if no direct evidence has been supplied as yet.* The average amount consumed daily ranges from 4-8 mg. in Britain to 15 mg. in the U.S.A. and Canada;[17] the chief sources are whole bread, cereals, green vegetables, dairy products and fish.

The site of absorption is not well established, but it is known that fats and bile facilitate absorption. The oral route is more effective than the parenteral.[18] It has not been established whether the vitamin undergoes a chemical change during the absorption process, perhaps resulting in an oxidation product, α-tocopheryl hydroquinone.[19] The blood level of α-tocopherol averages 1-2 mg. %, with wide individual variations: it is higher in old age and pregnancy and considerably lower in newborn and infants. Cerebrospinal fluid is devoid

*Very recent observations based upon red cell resistance to hæmolysis suggest that requirements in humans are at least 15 mg. daily, while in subjects with depleted reserves, the requirement might be higher than 30 mg./day(10).

of α-tocopherol, and there is little or no urinary excretion in rats or humans.[20] Milk and colostrum contain a significant amount of vitamin E; the average level in human milk is 15 times higher than in cow's milk, a fact which might be taken into account in investigations of the etiology of hæmolytic diseases in artificially fed infants.

Storage of vitamin E in human tissues at various ages has recently been studied by Dju and collaborators.[21] Very low at birth, the α-tocopherol level reaches maximum values in liver, skeletal muscle and heart during late childhood and adolescence; this high level is maintained throughout youth and adult life and later diminishes gradually, so that in old age it approaches the level noted at birth. Dju and collaborators established that the highest content in human tissues is in the pituitary, testes and adrenals, followed by fat. Infectious diseases and chronic alcoholism lower the α-tocopherol content of tissues. The same pattern of α-tocopherol content was noted in animal tissues; there is a significant difference in the concentration of vitamin in perigonadal fat, which is considerably richer in the vitamin than are perirenal and subcutaneous fats.

The participation of α-tocopherol in metabolic processes apparently takes place to a great extent in muscle; the mode of action and biochemical processes involving vitamin E are unknown, but indirect evidence gathered from experiments on animals deficient in vitamin E suggests that α-tocopherol might act as a co-factor or activator of the sequence of enzymatic reactions occurring during glycolysis or oxidative phosphorylation. Besides the already mentioned role as co-factor assigned to α-tocopherol in cytochrome-C reductase, recent findings show a significant decrease of α-ketoglutaric dehydrogenase and ATP in vitamin E deficient rats, and older experimental evidence shows beyond any doubt that administration of α-tocopherol dramatically diminishes the urinary excretion of creatine in rats with experimental dystrophy, thus healing and preventing this disease.[22]

Other metabolic routes are probably influenced by α-tocopherol, but experimental data are incomplete and sometimes conflicting. Better established is the detoxifying action of vitamin E, a factor which explains hepatic necrosis in deficient animals. Protein elaboration is influenced by α-tocopherol to a certain extent: deficient animals show a failure to synthesize proteins,[23] while rats treated with high doses of α-tocopherol exhibit an increase of gamma globulins in serum proteins and a corresponding hyperactivity of the Kupffer cells of the liver.[24]

The metabolism of fats is significantly influenced by vitamin E, whose protective action upon unsaturated fatty acids has caused a recent resurgence of interest, largely because of the accent placed upon the role of essential fatty acids in atherosclerotic disease. Apparently, vitamin E deficient rats have a diminished level of cholinesterase and lipase in serum, muscle and liver.[25] The pattern of distribution of lipids is changed in liver and serum: neutral fats decrease in favour of lipoproteins in deficient mice,[26] while a moderately high daily intake causes the opposite. Serum lipoproteins seem to be influenced by high amounts of α-tocopherol in rats;[24] α-lipoproteins diminish considerably and sometimes are absent, without any noticeable change in serum total cholesterol level.

The relationship between cholesterolæmia and α-tocopherol level is by now another problem in the limelight of metabolic processes in atherosclerosis. Administration of daily doses of 30-600 mg. of α-tocopherol to humans did not affect plasma cholesterol levels in controls[27] or in cases of myocardial infarction.[28] Higher doses, in the range of 1000 mg. a day, induce a moderate diminution of plasma cholesterol in normal adults,[29] while very high doses, in the range of 40,000 mg. a day (or 500-600 mg./kg. body weight), induce a definite lowering of all plasma lipid levels according to Greenblatt.[13] However, experiments in progress by Boyle[30] seem to show a "rebound phase" after a first significant lowering of serum cholesterol in patients treated with daily doses of 1600 mg. Other investigators[31] noted a cholesterol-lowering effect exerted by combined administration of low doses of α-tocopherol (300 mg. daily) and vitamin A in high doses (225,000 units daily) to atherosclerotic patients.

The necessity of administering enormous doses, such as 40,000 mg. a day, to lower plasma lipid levels enforces a certain caution before larger-scale clinical trials with this procedure are undertaken; indeed, this dose is in the range of that used by Borcelli and Prosperi in the experiments on hypervitaminosis E. More important seem to be the findings of Telford[32] in this matter; indeed, this author noted a significantly greater incidence of induced lung tumours in mice of hereditary lung-tumour strain, subjected to a daily excess of α-tocopherol, in the range of 100 mg./kg. body weight for seven months. However, the author suggests that this might be due to poorer absorption of the injected carcinogen rather than to a direct action of the excess of vitamin E. For the time being, this should not be interpreted as more than an experimental finding, without extrapolation to human pathology.

Nevertheless, all these results combine to stress the importance of acquiring more knowledge of the mechanism of action of α-tocopherol, in order to have an adequate basis for dosage. In the study of the relationship between cholesterolæmia and α-tocopherol, it might be noted that doses have varied between 30 mg. and 40,000 mg. daily in humans, or a maximum dose 1300 times the minimum administered. No reliable conclusions can be drawn under such disparity of experimental conditions. The storage life of α-tocopherol in tissues is another factor of error in the interpretation of

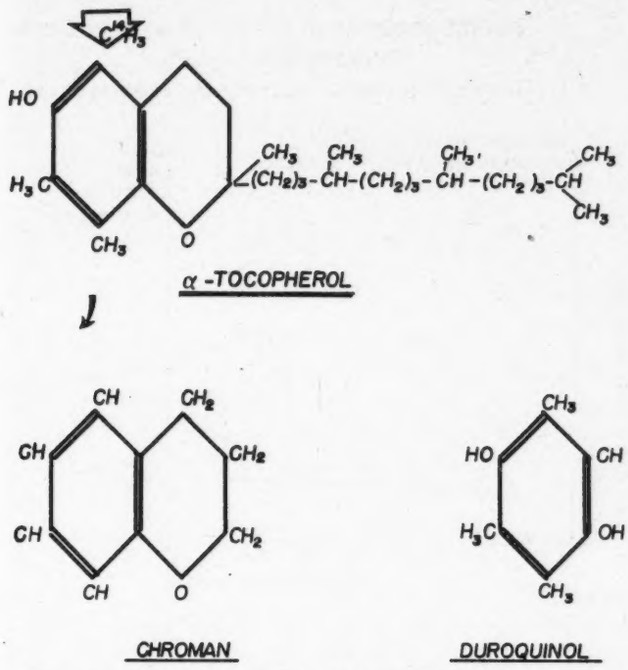

Fig. 2.—Structural formula of C14 α-tocopherol labelled in position 5-methyl. Chroman and duroquinol represent the related compounds.

results; there is no means of discovering the reserves of vitamin E, unless chemical determination is performed on the tissues.

Labelled Alpha-tocopherol

The possibility of using labelled α-tocopherol offers considerable advantages in the study of the metabolic pathway of the vitamin. This procedure offers an immediate means of estimating the turnover in tissues, the length of repletion or depletion time, and most important of all, the pathway of the vitamin in terms of well-established parameters.

Radioactive α-tocopherol has been synthesized by Baxter and associates,[33] with C^{14} placed in the CH_3 group as seen in Fig. 2 The radiochemical purity has been estimated by the author as being over 99% of the product, and the stability of the tagged atom is great enough to offer reasonable security that no passive exchange will occur between the C^{14} of the vitamin and stable carbon of the environment, without metabolism of the vitamin. Labelled α-tocopherol has reasonably high radioactivity, so that a physiological dose in the range of 500 μg. per animal (3-5 mg./kg.) can be detected with accuracy in the assayed portions of tissues. Radioactive vitamin E was used in rats by Niedner and Conner Johnson[34] but only fragmentary data were published and no information regarding the amount given to the animals was available. The animals were given labelled vitamin by the oral or intraperitoneal route and their excreta and tissues assayed for C^{14}, 48 hours after administration of α-tocopherol. There is some excretion in the expired CO_2 and the urine, but most of the radioactive material is excreted through the fæces; no significant difference has been noted between normal and vitamin E deficient rats in this respect.

TECHNIQUE

Labelled α-tocopherol succinate was administered orally to rats in physiological amounts (0.5 mg./animal) or in pharmacological doses (50 mg./animal, containing only 0.5 mg. radioactive vitamin). The vitamin was emulsified with one drop of Tween 80 in 50 ml. distilled water, and 1 ml. of the emulsion was given by intragastric tube to fasting rats weighing 150 g. The animals were previously kept on a Purina Chow diet, which ensured a reasonable supply of vitamin E, so that no latent deficiency was possible. After administration of the vitamin, no food was allowed for 4-5 hours, in order to maintain the same conditions of gastric absorption. The animals were killed by aortic puncture after a light ether-induced drowsiness at intervals ranging from one hour to 192 hours after ingestion. At various moments, the expired air was collected in a closed air system and the radioactivity of its CO_2 content assayed. The excreta and the great majority of the tissues were assayed for their C^{14} content; serum lipoproteins were analyzed by a thick paper electrophoresis procedure and their C^{14} content was assayed. The digestive tube was sectioned throughout its whole length in equal portions of 1 in. (2.54 cm.) and the radioactivity of the wall portions and the content was assayed. No attempt was made to corroborate radioactivity data by chemical or chromatographic determination of tocopherols, since the problem investigated was primarily a study in function of time, rather than chemical identification of the catabolic products.

RESULTS

I. *Physiological doses in rat* (0.5 mg./animal in one dose).

(a) *Absorption of α-tocopherol in function of time.*

The results are presented in Fig. 3, which shows the curve of the total radioactivity of stomach and intestine contents. Radioactivity is expressed as a percentage of the total ingested C^{14}-labelled α-

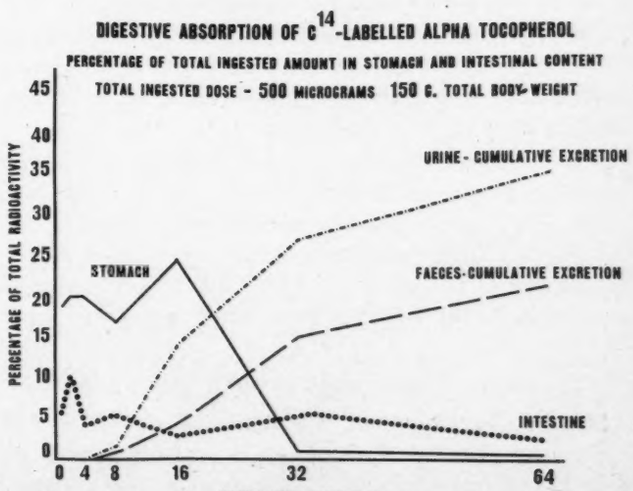

Fig. 3.—Digestive absorption of labelled α-tocopherol. Study in function of time.

tocopherol. Each point of the curve represents the average value of five animals; in order to simplify the figure, the range is not presented. The following facts are noteworthy:

1. The largest amount of radioactivity is found in the stomach contents, in which an average of 16-24% of the total ingested α-tocopherol remains for as long as 16 hours after ingestion. The intestinal content averages 5% of the total ingested vitamin, the highest value not quite reaching 10%.

2. The study in function of time leads to a surprising conclusion. Not only is the stomach content the highest, but after having diminished slightly (19.12% at one hour as against 16.87% at 8 hours), it reaches its maximum value 16 hours after ingestion (23.82%). The radioactivity then drops sharply to 0.95% at 32 hours and 0.11% at 64 hours. The curve for intestinal contents has a rather flat aspect, the value at 32 hours being equal to that at one hour after ingestion (5.86% and 5.65%).

Persistence of a highly radioactive stomach content long after termination of the normal digestion process could be attributed either to inhibition of the absorption process or to re-secretion of the already absorbed vitamin. Inhibition of absorption is often noted after intake of large amounts of fat or of Tween 80; this was not the case in our studies, for the amount of Tween 80 was only one drop per 50 ml. water and the stomach fat content was almost negligible during the first four hours after ingestion, when the animals were kept fasting. The possibility of *adsorption* of the radioactive vitamin in a molecular layer on to the cells of the mucosa was investigated, but the results pointed to the presence of radioactive material *in* the stomach content. Thus it must be concluded that this persistence is more in accordance with a re-secretion cycle in the stomach, perhaps leading to a concentration several times that in the blood. This phenomenon is not at all unique; it has been noted in the pre-thyroid phase of the radioiodine pathway after oral administration: indeed, the ingested iodide is rapidly absorbed through the gastric mucosa in 15-30 minutes, and is re-secreted in the gastric juice, saliva and milk in the next few hours, reaching a concentration 30-40 times higher than that in the blood.

(3) Radioactivity appears in the fæces eight hours after ingestion when 0.69% of the ingested amount is detectable. The cumulative value reaches 20.53% 64 hours after ingestion and remains at a steady level for at least 192 hours (0.10% fæcal excretion in the last 96 hours after ingestion).

(b) *Site of digestive absorption of α-tocopherol.*

The radioactivity of the walls of the digestive tract was assayed throughout the whole length of the digestive tube, and in some cases the mucosa, muscle coats and serosa were assayed separately. The results are presented in Fig. 4.

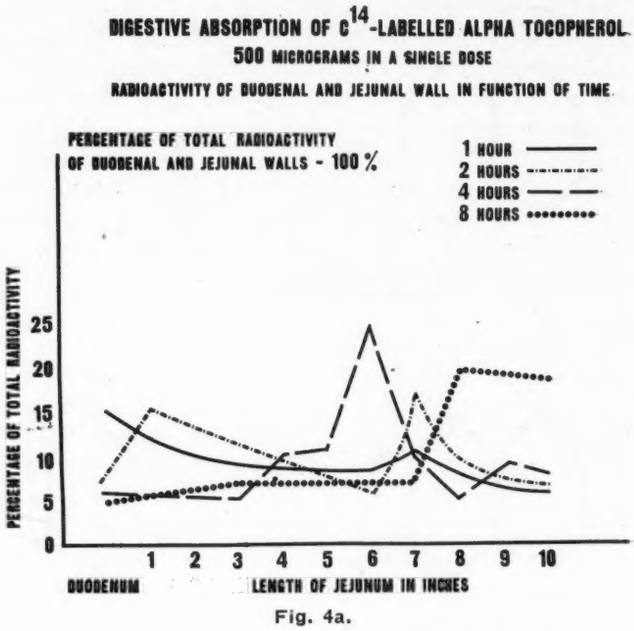

Fig. 4a.

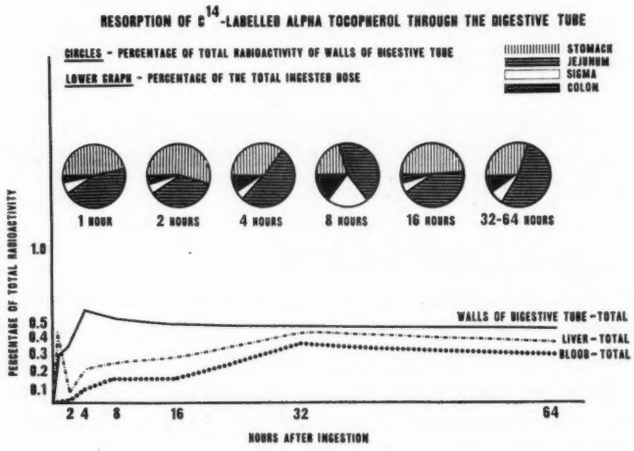

Fig. 4b.

Fig. 4.—Radioactivity of the walls of the digestive tube. (a) Study in function of the length of the digestive tube. (b) Study in function of time after ingestion.

The total amount of C^{14} in the walls of the whole digestive tract on the average stands at a level far lower than that of the content: 0.329% at one hour and 0.623% at four hours as against 24.58% and 24.77% respectively for contents. This might be interpreted as evidence against a longer stay of α-tocopherol in the digestive cells, in a manner similar to that of the passage of iron and its binding to ferritin in these cells. Apparently, there is no saturation limit for α-tocopherol absorption.

Analysis of the radioactivity of walls in function of time points towards a maximum of absorption between four and eight hours after ingestion, followed by a slow diminution; however, the spread between the minimum and maximum is small. The transit is almost equally distributed between stomach walls and the jejuno-ileum, the stomach being more active in the first four hours, while the jejuno-ileum assures absorption afterwards. At the moment of maximum absorption, there is a significant increase of radioactivity in the walls of the

large bowel, sigmoid and colon, the radioactivity of the sigmoid walls averaging 26.0% of the total C^{14} content in the digestive walls and 13.4% in the colon. At other intervals during the examination, the radioactivity of the sigmoid walls averages 5-9% and that of the colon 2.7-8% of the total.

In terms of grams of tissue, the concentration of C^{14} is practically the same, regardless of the region of the digestive tube examined; this would imply that the process of absorption of vitamin E is independent of the pH of the digestive tube content, since it is the same in the acid medium of the stomach as in the alkaline medium of the jejuno-ileum. Vitamin E is absorbed well in the absence of bile, for the rate of absorption in the stomach where bile is absent is the same as that in the jejunum or ileum where bile is present. This independence of bile is even more important than the indifference to pH. This is another finding at variance with those established in experiments with stable vitamin E: some authors have shown that absorption in rats and in dogs requires the presence of bile.[35]

(c) *Transport of α-tocopherol in blood.*

Fig. 5 shows the electrophoretic pattern of lipoproteins in portal and aortic serum and the radioactivity assay of the separated fractions.

1. No significant difference between the radioactivity of portal and of aortic serum was noted at any moment during the experiment. This fact implies that after a physiological dose, the passage of α-tocopherol through the liver is not followed immediately by its storage in this organ. Moreover, the radioactivity of the liver is in the same range as that of the blood.

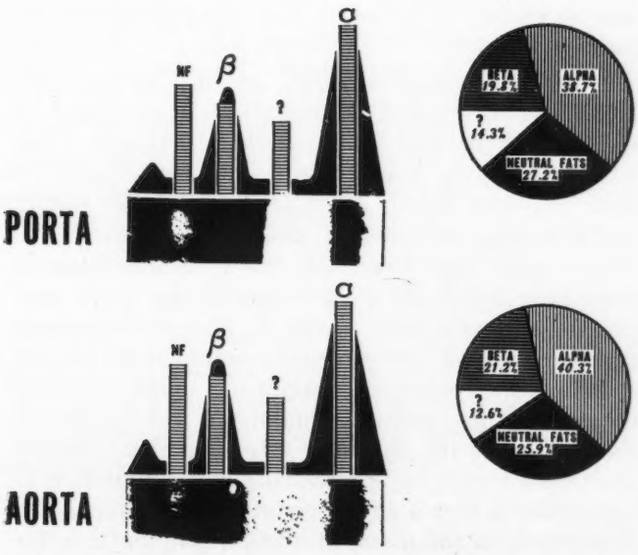

Fig. 5.—Distribution of radioactive C14 in the lipidic fractions of aortic and portal serum of rat.

Left: Lipidogram obtained by cardboard electrophoresis with prestained serum. The columns are proportional to the radioactivity assayed in each fraction. The curves are proportional to the eluted stain (Acetylated Sudan Black).

Right: Per cent distribution of radioactivity, total amount per ml. serum: 100%.

2. The distribution of C^{14} containing material among the lipid fractions is 27.5% in the neutral fat fraction and 58.4% in the lipoproteins; some 14.1% seems to be linked to a fraction situated between the two lipoproteins, perhaps the α_2 globulin; however, more data are necessary for this last assumption. No vitamin E was found in the albumin fraction, despite the facility with which this fraction binds α-tocopherol *in vitro*.

3. Analysis of serum concentration of α-tocopherol in function of time shows that labelled material appears in serum as early as one hour after ingestion, yet in a very low concentration (0.018%); there is a level of 0.10-0.15% between 4 and 16 hours and an even higher one at 32 hours (0.366%). The concentration of labelled material diminishes to very low levels 192 hours after ingestion.

(d) *Excretion.*

Analysis of expired CO_2 failed to reveal the presence of any radioactive carbon during the experiment. This does not necessarily imply that the vitamin does not undergo a complete catabolism, leading to CO_2 formation, but only that the CH_3 group in position 5 either remains attached to the ring or follows another metabolic pathway. The air was collected only for short periods, and not later than 24 hours after ingestion. Thus it was not possible to confirm the findings of Niedner and Conner Johnson,[34] who found 1.20%-1.50% of the ingested C^{14} in the expired air 48 hours after ingestion.

More revealing is the examination of the curve of urinary excretion of radioactive material. Indeed, the level in urine, devoid of radioactivity for the first four hours, averages 1.41% eight hours after ingestion, rises sharply to 14.56% at 16 hours (cumulative curve) and maintains the same gradient for the next 64 hours (37.90% cumulative excretion at 64 hours). The cumulative curve of urinary excretion does not resemble that of fæcal excretion, studied above; its rate steadily increases, while that of fæcal excretion reaches a steady state after 64 hours. Moreover, the total amount of radioactivity in the excreted urine equals and sometimes exceeds that in the fæces. This is at complete variance with the reports in the literature, even those based on data obtained with labelled α-tocopherol, where urinary excretion is stated to be very low, in the range of 1% of the total. At first these results seem surprising, but they can be interpreted as due to excretion of an inactive form of α-tocopherol, having lost both its biological potency and its chemical specificity. Radioactive isotope procedures have permitted the identification of a similar inactivation product excreted through the urine on ingestion of Co^{60} labelled vitamin B_{12}: the inactive labelled compound has been identified as a hydroxy derivative of vitamin B_{12}, impossible to trace until then. Whether the urinary C^{14} in the case of α-

tocopherol represents a derivative similar to α-tocopheryl hydroquinone or a more advanced product of catabolism, will be established only by chromatographic analysis. For the moment, it is sufficient to suppose that the urinary excretion represents an index of tissue utilization of *circulating* vitamin E, whereas the fæcal content is an index of the *unabsorbed* vitamin; this might account for the differences in gradient of excretion curves of these routes: the unabsorbed excess is eliminated during the first three to four days, while the circulating vitamin is slowly metabolized at a constant rate, until the supply is exhausted.

(e) *Storage and distribution in tissues of normal rat.*

Fig. 6 shows the distribution of radioactive vitamin E in the tissues of rat 24 hours after ingestion of 0.5 mg.

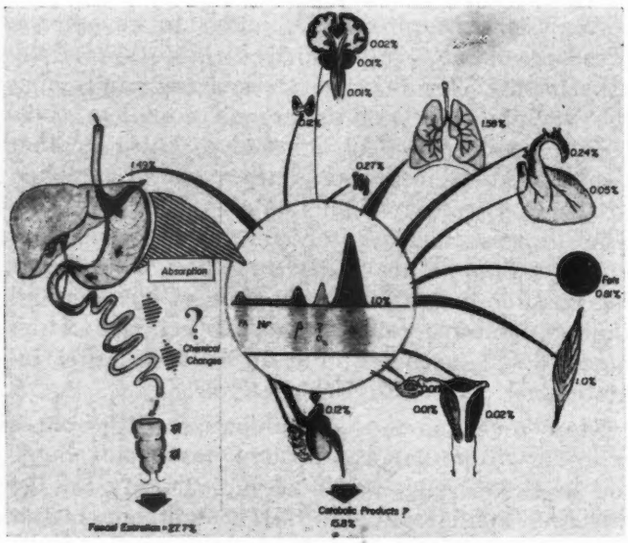

Fig. 6.—Metabolic pathway of physiological amounts (0.5 mg.) of C14-labelled α-tocopherol in adult rat.
The thickness of the arrows is roughly proportional to the quantitative importance of the phenomenon represented.
The figures near the schema of organs symbolize the percentage of ingested vitamin found in the whole organ at 24 hours after ingestion.

In addition to the figures already presented for fæcal and urinary excretion (in this case totalling 42%), the content of the digestive tube accounts for 28.5%; thus only 30% of the ingested vitamin was in circulation and distributed at 24 hours. The highest concentrations at this time are found in lungs (1.58%), skeletal muscle (1.35%) and liver (1.49%) (Fig. 6). In the range of 0.1% and in decreasing order are bone marrow, adrenals, thyroid, plasma, aorta, heart, spleen and kidney. Far less concentrated, in the 0.01% range, are gonads and sexual fat, brain, cerebellum and spinal cord. There was no detectable labelled material in the pituitary.

The ratio erythrocyte/plasma of C^{14} α-tocopherol ranged from 0.25 to 0.35, similar to that found in the case of stable α-tocopherol. The walls of the digestive tube account for 1.12% of the total radioactivity, suggesting that the absorption process is still very active 24 hours after ingestion. Some of these results are again in conflict with those obtained with the aid of stable α-tocopherol, such as the very low concentration of radioactive vitamin in the pituitary or the perigonadal fat, as opposed to the very high concentration of vitamin E in these tissues found by Dju.[21] These data are not at all contradictory, if one remembers that investigation with labelled compounds gives information about the turnover rate of the compound and not the total amount as determined by chemical procedures. Viewed in this light, the above figures indicate that the turnover rate in the pituitary, fat, nervous system and gonads is far slower than in muscle, lungs and liver. The concentration curve given for the liver in function of time is somewhat different; an inexplicable maximum is recorded during the first hour, followed by a slow rise to a second maximum at 32 hours. The slope of the second curve points to an estimate of the half-life of α-tocopherol in liver, of about 45-50 hours; the half-life of serum α-tocopherol seems to be somewhat longer, being in the range of 60 hours, but more precise data will be given later, when chemical determinations are superimposed on radioactivity assay. This turnover time can be compared with that of other metabolites: testosterone (10-30 minutes), triiodothyronine (4-6 hours), thyroxine (7-9 days), cholesterol (10-12 days). No comparable data for the half-life of other fat-soluble vitamins are available in literature.

(f) *Sex and age differences in tissue distribution of labelled vitamin E.*

This subject will be treated in detail in another paper dealing with turnover modifications of α-tocopherol in experimentally induced hormonal modifications: however, a few data might be of interest, namely:

1. In mid-gestation 1.29% of the ingested C^{14} labelled α-tocopherol in animals is transferred to the egg in the first 24 hours after ingestion. This is shared among fetus (0.56%), placenta (0.45%) and amniotic fluid (0.27%). A relatively higher concentration of labelled vitamin is noted in the ovaries and the uterus of the gestating animal, averaging levels 20 to 40 times those in a non-pregnant female rat. There is also an increased turnover rate of α-tocopherol contained in the fat of the same order of magnitude. This dramatic increase is in contradistinction to the moderate diminution of the turnover rate in skeletal muscle and leads to the hypothesis that rapid depletion of α-tocopherol stores in pregnant animals imposes a diminution of the tissue utilization rate and a faster replenishment of the reserves, leading to a more rapid transfer to the fetus. The same phenomenon is noted early in the lactation period of animals in which muscle turnover of vitamin E is even slower and transfer of labelled α-tocopherol in milk to

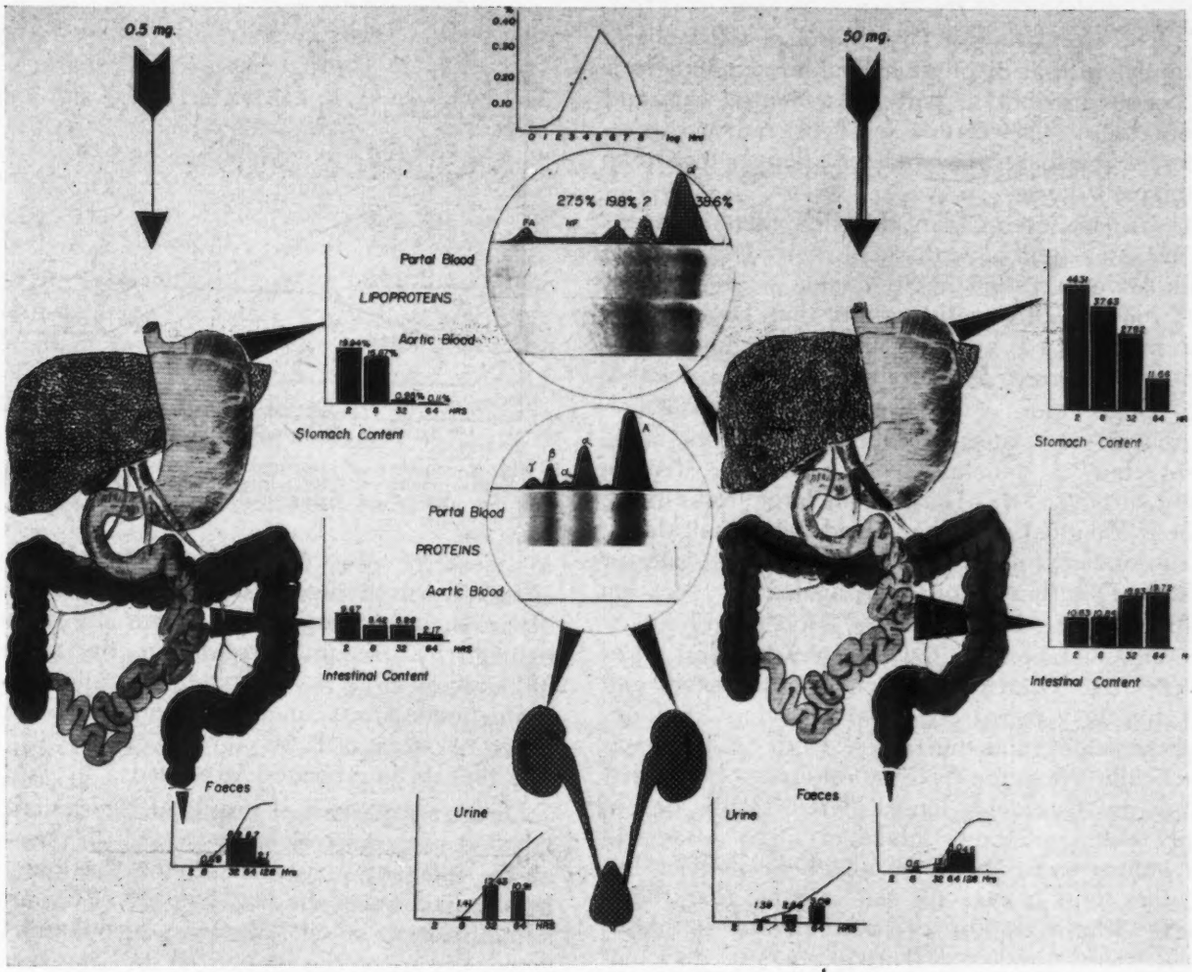

Fig. 7.—Digestive absorption of labelled α-tocopherol. Comparison between 0.5 mg. and 50 mg. in a single ingestion. Curve of gastric and intestinal content in function of time.

sucklings averages 4.05% of the ingested vitamin in 24 hours.

This is in complete accordance with the knowledge already acquired of the physiological role of vitamin E during pregnancy: acceleration of turnover rate allows faster depletion of the storage sites, thus ensuring faster transfer to fetus or suckling. When stores are exhausted, deficiency signs appear in tissues where the increased turnover is most significant, i.e. in the uterus. Perhaps this is the reason why the first finding of vitamin E deficiency was the degeneration of uterine muscle followed by absorption of the ovum.

2. There is no apparent difference between the metabolic pathway of labelled α-tocopherol in female and male rats, nor do older animals show any striking difference from the adult ones. However, more data are necessary in order to obtain a complete picture in this matter.

II. *Pharmacological doses of α-tocopherol* (50 mg./day/animal).

Comparison between metabolic pathways of physiological and pharmacological doses of α-tocopherol in the rat is illustrated in Fig. 7. The chief points are the following:

1. Large amounts modify the usual pattern of absorption of α-tocopherol in that the stomach contains a higher level of radioactive vitamin (46.31% at 2 hours, 37.63% at 8 hours, 28.02% at 32 hours and 11.66% at 64 hours) for a longer period of time. There is still more than one-quarter of the ingested vitamin in the stomach content 32 hours after ingestion, and one-tenth after 64 hours. Of course, there is the possibility of error due to a difference in the pathways followed by the stable and by the labelled vitamins, but this is improbable. The intestinal content is similar to that noted in physiological doses for the first two hours, and then it increases gradually, suggesting a greater excretion of the unabsorbed vitamin. The same effect is shown by the curve of fæcal excretion, which shows a slower rise and greater persistence than its physiological counterpart. The plateau noted previously is reached in 96 hours, instead of 32 hours. Thus, a high dose of vitamin E remains longer in the stomach and the intestines, but the proportion of unabsorbed vitamin does not increase as much as expected from data obtained with stable α-tocopherol.

2. There is no modification of the site or of the rate of absorption, the radioactivity of the walls of the digestive tube being practically the same after ingestion of small or large doses.

3. The circulation of large doses of α-tocopherol is similar to that of physiological amounts; there is the same distribution pattern in neutral fats and lipoproteins. The serum level of radioactive α-tocopherol remains elevated for a longer time than with small doses.

4. Urinary excretion of labelled material starts at the same time as with small doses; the curve of cumulative excretion has the same slope but persists longer. This fact suggests that larger doses are metabolized at the same rate, metabolism continuing longer because the supply is assured.

5. Distribution of large amounts of labelled α-tocopherol in tissues is similar to that of small doses, but in general the storage sites show a faster turnover rate. The rate for large doses in the liver is identical with that noted with small doses; the secondary role of the liver as a storage site for vitamin E is thus emphasized again.

In summary, large doses of α-tocopherol follow the same metabolic pathway as physiological doses in the rat. Gastric retention is prolonged and quantitatively increased, fæcal excretion continues slightly longer, and the rate of tissue utilization is practically the same, the only difference being that supply is assured for longer. These results do not imply that continuous intake of large doses will not induce a change in the metabolic pattern, but for the time being one can assume that therapeutic administration of α-tocopherol in doses larger than physiological requirements does not disturb the metabolic pathway of the vitamin, but only ensures a steady supply and perhaps a continuous circulation through the gastric reservoir.

The knowledge acquired by the present investigation is summarized in Fig. 7, which is constructed in the same manner as Fig. 1, and based upon data obtained from the literature.

The comparison between physiological and pharmacological doses is summarized in Fig. 8.

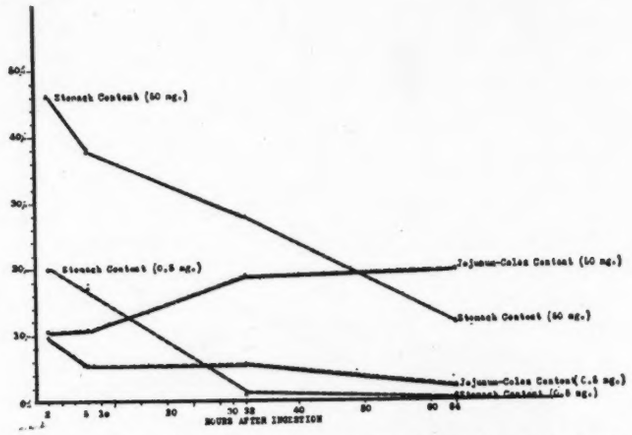

Fig. 8.—Digestive absorption of C14-labelled α-tocopherol. Comparison between physiological and pharmacological doses (500 μg. and 50 mg.). Ingested dose = 100%.

APPLICATIONS OF THE ABOVE

The results of these animal experiments provide some information which can be of immediate practical value to the clinician. Firstly, knowledge acquired by the use of labelled α-tocopherol in rats show that absorption of the vitamin from the stomach is as important as, or more important than, absorption from the intestine, from the points of view of both quantity and duration. Secondly, the metabolic fate of a single large dose of vitamin E is apparently similar to that of a physiological dose. This possibly answers the question often raised by physicians whether large doses of α-tocopherol lose their vitamin action and behave in the manner of a drug rather than a vitamin. If the results obtained in the rat after a single large dose of vitamin E could be extrapolated to humans, and were valid for many large doses, then these results might be a point in favour of the advocates of high doses of α-tocopherol in therapy. Thirdly, in view of the trend in atherosclerotic diseases towards giving diets containing large amounts of unsaturated fatty acids, which are subject to damage by irreparable oxidation, the persistence of α-tocopherol in the stomach might act as protection against such oxidation; logically, high doses of vitamin E should be given with every diet high in unsaturated fatty acids.

Direct comparison of results of experiments with labelled α-tocopherol in rats and in humans is at the moment very difficult, for the low energy beta radiation and the long half-life of C^{14} preclude administration of C^{14} labelled α-tocopherol to humans. We are in the process of studying two other labels (Hg^{200} and Cl^{38}), both of which are gamma emitters and potentially applicable in humans. Only after the completion of these experiments will it be possible to compare the experimental data obtained in rats to the mechanism of action in humans.

CONCLUSIONS

Physiological amounts of C^{14}-labelled α-tocopherol administered orally to rats remain for a long time in the stomach, suggesting a cyclic process of re-secretion of the vitamin through the stomach mucosa. There is no specific site of absorption of the vitamin, whose passage through the walls of the digestive tract seems to be independent of the pH of the medium and of the presence of bile. Fæcal excretion of radioactive material occurs during the first 24-36 hours, and represents almost exclusively unabsorbed vitamin. There is no respiratory excretion of labelled CO_2 for the first 24 hours after ingestion of $C^{14}H^3$-labelled α-tocopherol in position 5.

Radioactive α-tocopherol appears in the serum in the first hour after ingestion, and persists for 64 to 96 hours. In serum, the vitamin is distributed among neutral fats and lipoproteins, the α fraction being comparatively richer than the β. There seems to be some labelled material bound to the α_2 globulin. The half-life of α-tocopherol in the serum of the adult rat is in the range of 60 hours.

Radioactive α-tocopherol is excreted in the urine as early as eight hours after ingestion, and excretion continues for a longer period of time than does fæcal excretion. The labelled material excreted in urine is probably a catabolic product of α-tocopherol, which has lost its biological and chemical properties. The study of urinary excretion rate of labelled α-tocopherol offers information regarding the rate of utilization of the vitamin by the tissues.

The turnover rate of α-tocopherol is in the range of 45-50 hours in the liver and possibly in the same range in skeletal muscle, heart, lungs and walls of the digestive tract. It is considerably slower in fats, nervous system, adrenals and pituitary.

Pregnancy and lactation significantly increase the turnover rate of α-tocopherol in fats, ovaries and uterus, and slightly decrease the turnover rate of the vitamin in skeletal muscle. There is a significant transfer of α-tocopherol to placenta, amniotic fluid, fetus and milk at 24 hours after ingestion of labelled α-tocopherol.

When a single oral dose 100 times larger than the daily physiological requirement for the rat is given, the metabolic pathway of labelled α-tocopherol is not grossly altered, but the stomach content remains radioactive for a longer time and its radioactivity is higher, suggesting that high doses undergo repeated re-secretion through the gastric mucosa, thus ensuring a continuous supply of vitamin. Fæcal excretion of radioactivity is not significantly increased; it is prolonged by only a few days. Urinary excretion is also prolonged, suggesting that utilization of vitamin by the tissues can continue for a longer period. There is no change in the tissue distribution pattern of the vitamin, nor is the turnover rate in the serum modified by a single intake of a large amount of vitamin E.

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RÉSUMÉ

Une dose physiologique de vitamine E marquée au C^{14} dans la position 5-méthyle, administrée par voie orale au rat adulte, demeure longtemps dans le contenu gastrique, et suggère un processus de resecrétion de la vitamine après résorption. La résorption de la vitamine E semble être indépendante du pH du milieu, ainsi que de la présence de bile, car elle se fait avec la même intensité à travers les parois du tube digestif de l'estomac à l'iléon. L'excrétion fécale de matériel radioactif se produit surtout au cours des premières 36 heures après l'ingestion et représente presqu'exclusivement le taux de vitamine non absorbée. Il n'y a pas d'excrétion de CO^2 marqué pendant les premières 24 heures après ingestion de vitamine E marquée au C^{14}.

L'ingestion d'α-tocophérol marqué au C^{14} est suivie d'une apparition de radioactivité dans le sérum dès la première heure, et durant environ 64-96 heures. Le matériel radioactif est distribué entre les graisses neutres et les lipoprotéines, les lipoprotéines α étant comparativement plus riches en α-tocophérol que les lipoprotéines β. La demi-vie de la vitamine E dans le sérum du rat adulte est d'environ 60 heures.

L'urine devient radioactive huit heures après ingestion d'α-tocophérol marqué au C^{14} dans la position 5-méthyle. L'excrétion de matériel radioactif continue pendant une période de temps plus longue que l'excrétion de radioactivité dans les fèces. La nature exacte du produit radioactif excrété dans les urines est inconnue, mais il semble qu'il s'agit d'un dérivé catabolique de la vitamine E, qui a perdu ses propriétés biologiques et chimiques, ce qui le rend impossible à déterminer par les méthodes classiques. L'étude de la courbe d'élimination urinaire de radioactivité après ingestion de vitamine E marquée peut permettre l'établissement d'une méthode d'appréciation de l'utilisation tissulaire de la vitamine.

La vitesse de turnover de la vitamine E marquée est d'approximativement 45-50 heures dans le foie, et peut-être du même ordre dans les muscles, le myocarde et les poumons. Le turnover est considérablement ralenti dans les graisses, le système nerveux, les surrénales et l'hypophyse.

La grossesse et la lactation accélèrent notablement le turnover dans les graisses, les ovaires et l'utérus, et produisent, par contre, un léger ralentissement dans les muscles. La vitamine E est transférée en quantité appréciable dans le placenta, le fœtus et le liquide amniotique, dans les premières 24 heures après ingestion de vitamine par la mère.

Le métabolisme d'une dose unique de vitamine E 100 fois plus grande que celle qui représente les besoins quotidiens du rat adulte est le même que celui des doses physiologiques. Cependant le contenu gastrique demeure radioactif plus longtemps et à un niveau plus élevé; ceci suggère le présence d'un processus cyclique de resécrétion de la vitamine à travers la muqueuse stomacale, processus qui paraît être un mécanisme supplémentaire de récupération de la vitamine, autrement destinée à être éliminée dans les selles. L'élimination fécale des doses fortes est prolongée de quelques jours, mais elle n'est pas considérablement augmentée. L'excrétion urinaire est prolongée, suggérant une utilisation prolongée de la vitamine E par les tissus. La vitesse de turnover de la vitamine dans le sang n'est pas modifiée, celle du foie non plus. J.S.

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Case Reports

MULTIPLE SPIDER ANGIOMATA IN A PATIENT WITH KLINEFELTER'S SYNDROME*

C. G. ROLAND, M.D., A. G. ROGERS, M.D. and R. G. D'AGINCOURT, M.D.,
St. Boniface, Man.

IN 1942, Klinefelter, Reifenstein and Albright[13] described a syndrome characterized by gynæcomastia, small testes and aspermatogenesis, with normal Leydig cells. The only significant hormonal alteration discovered in their nine patients was an increase in urinary excretion of pituitary gonadotrophins. Testicular biopsies obtained from seven of the patients showed hyalinization of the seminiferous tubules with essentially normal interstitial cells.

Heller and Nelson,[11] in 1945, pointed out that similar clinical findings could be observed in many patients without gynæcomastia. As a result of their findings, patients with the syndrome were reclassified into three clinical groups: "eunuchoid", "moderately eunuchoid" and "normal". They further suggested that clinical evidence of decreased Leydig cell function may be found in patients having Klinefelter's syndrome; many of their cases showed some degree of "aleydigism",[18] and some evidence was presented suggesting a positive correlation between this finding and the presence of gynæcomastia. "Sclerosing tubular degeneration"[12] and "ovarian dysgenesis"[24] are suggested synonyms.

The publications of Barr, Moore and their coworkers relating to the apparent sexual specificity of cellular nuclear masses have resulted in a clarification of the Klinefelter syndrome. Approximately four out of five cases classified clinically and histologically as having Klinefelter's syndrome have chromatin-positive nuclei,[3, 10, 15, 24] that is, stained mucosal smears or tissue sections will show sex chromatin masses (Fig. 1) in from 40 to 70% of cells examined. This is true no matter which of the standard methods, recently reviewed by Rathbun, Plunkett and Barr,[20] is used.

It has become evident that a large majority of persons with Klinefelter's syndrome have female chromatin. These patients are termed by Nelson[15] examples of "true Klinefelter's syndrome". A minority who are genetically male are termed "false Klinefelter's syndrome". Witschi, Nelson and Segal[25] have coined the word "pseudo-male" to describe patients with true Klinefelter's syndrome.

Ashley and Jones[1] have pointed out that the true syndrome is an instance of complete sex reversal, the genetic sex revealed by examination of the cell nuclei being diametrically opposed to the phenotypic revealed by body habitus and the histological appearance of the gonad.

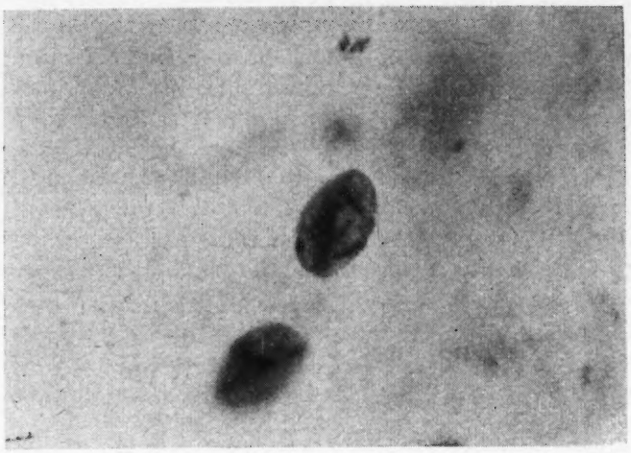

Fig. 1.—Photomicrograph showing a cell from the smear of this patient's oral mucosa. The sex chromatin mass is seen on the inner aspect of the nuclear membrane. (Cresylecht violet, × 2000.)

Dozens of cases of Klinefelter's syndrome are found in the literature. However, we have been unable to find any instance in which spider angiomata were particularly noted. We felt that the following case, in which the two conditions were co-existent, should be published.

A 32-year-old French Canadian was admitted to St. Boniface Hospital on March 14, 1958, for investigation of hæmatemesis. He had vomited once or twice a day for one week; the vomitus was streaked with blood. On admission his hæmoglobin value was 13.1 g. %. He was not in shock, and it was felt that he was not bleeding severely. Three weeks previously he had been admitted to another hospital because of hæmatemesis and epigastric pain, but left hospital without treatment.

On physical examination it was noted that the patient's build, while not eunuchoid, was somewhat feminine (Fig. 2). His voice was not high-pitched.

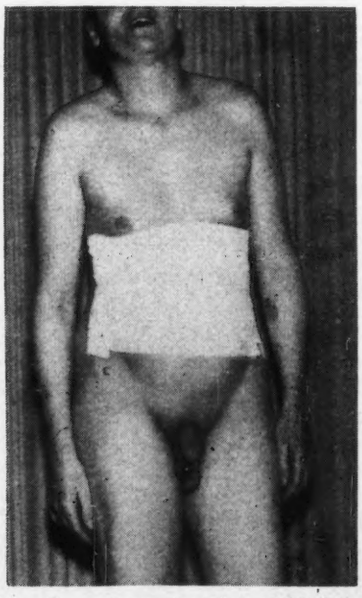

Fig. 2.—Note the gynæcomastia, widé hips, and small testes. Figs. 2, 3 and 4 were taken one week postoperatively, and this is the reason for the abdominal dressing and the absence of pubic hair.

*From the Departments of Medicine and Surgery, St. Boniface Hospital, St. Boniface, Manitoba.

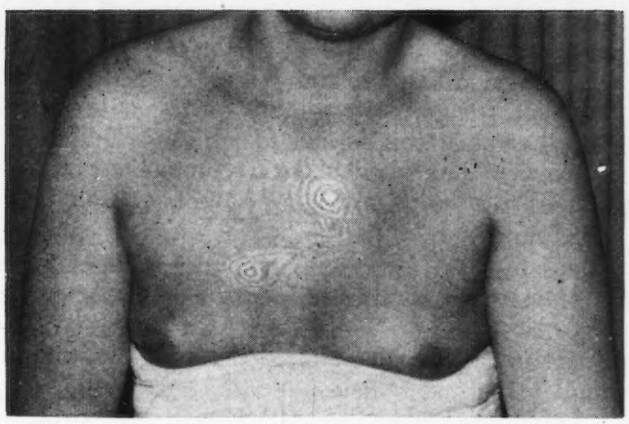

Fig. 3.—The gynæcomastia is evident here, and several spider angiomata can be made out around the left sterno-clavicular joint.

Facial hair was very sparse; a few dark hairs were seen on the chin and upper lip. Axillary hair was scanty. The pubic hair distribution was typically female. Numerous spider angiomata were found on the neck, shoulders, arms and hands. At least 26 were counted.

Moderately prominent gynæcomastia was evident when the patient sat up (Fig. 3). The breasts were soft, with no clearly defined glandular tissue palpable. The patient's blood pressure was 120/70 mm. Hg; pulse rate 80. Heart and lungs were normal. The abdomen was slightly distended, with mild generalized tenderness. Bowel sounds were active. The penis and scrotum appeared normal (Fig. 4). The testes were small, measuring 2.2 by 1.2 cm. each (normal figures are 4.5 by 2.5 cm.[9]). The measurements include scrotal tissue but not the epididymis. The prostate was questionably palpable.

The patient weighed 167 lb., was 70 inches (1.75 m.) tall and had a span of 70 inches. When he was standing erect the distance from pubic symphysis to floor was 33 inches, from pubis to cranium 37 inches.

His previous medical history included frequent convulsions between the ages of 12 and 16. At age 15, he had mumps complicated by severe pain and swelling of both testicles. In an automobile accident, in 1950, he received fractures to skull and limbs, and internal injuries.

The patient first experienced erection at age 16 or 17. He denied any difficulty in achieving erection, and claimed frequent sexual intercourse. He stated that his father and most of his brothers have, like himself, very scant growth of facial hair. His sisters, however, are said to be "hairy like men".

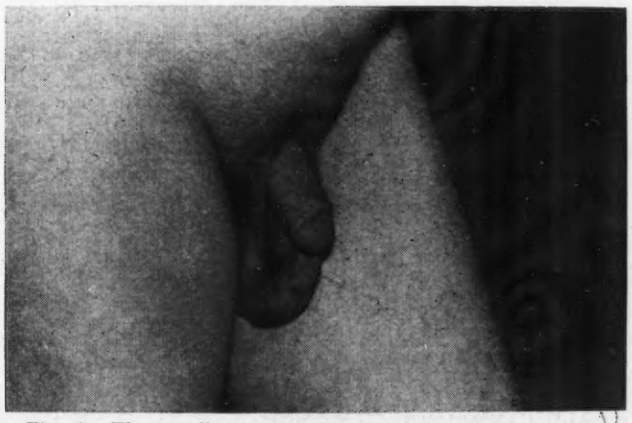

Fig. 4.—The small testes and apparently normal penis can be seen. Also, although the pubic hair has been shaved, the typically feminine distribution is evident.

His intelligence was in the low normal range. The discovery of frequent falsehoods in his admission history, and unconventional behaviour while in hospital, led us to request a consultation from the Department of Psychiatry. Dr. J. Matas believed that the patient could be considered as an example of pseudologia fantastica, because the details of his biography were obviously erroneous, extravagantly so, and of a type designed to put the patient in a better light.

Laboratory examinations.—The patient's hæmoglobin level, red and white blood cell counts, urinalysis and chest roentgenogram were all normal. A barium series revealed a normal œsophagus and stomach. The duodenal cap showed an ulcer deformity with no definite crater. The following liver function tests were performed, with results within the normal range in all cases: bromsulphalein retention; cephalin-cholesterol flocculation; thymol turbidity and flocculation; alkaline phosphatase; total bilirubin; and serum proteins.

The findings of gynæcomastia, spider angiomata and small testes and a previous history of convulsions led to a suspicion of Wilson's disease. This was excluded on the basis of normal results of tests of liver function, a normal blood uric acid level, and normal urinary excretion of copper.

The second diagnosis considered was Klinefelter's syndrome. A smear of the patient's oral mucosa was examined, and reported to be "chromatin-positive", 58% of cells examined having sex chromatin masses. Blood smears were examined for the presence of neutrophilic "drum-sticks". These were present in 8 of 85 consecutive cells (3 or more per hundred is considered to indicate a chromosomal female individual[7]).

TABLE I.

Test	*Normal males*	*This patient*
Urinary pituitary gonadotrophins.....	50 mμ or less/24 hrs.	+211 mμ/24 hrs. −316 mμ/24 hrs.
Urinary œstrogens.....	None detectable by the method used*	10.1 mcg. œstrone/24 hrs.
Urinary 17-ketosteroids...	10-20 mg./24 hrs.	4 mg./24 hrs.
Urinary 17-hydroxysteroids.....	6-19 mg./24 hrs.	2 mg./24 hrs.

*Extraction method: see Engel, *J. Biol. Chem.*, 185: 255, 1950. Spectroscopic method: see Brown, *Biochem. J.*, 60: 185, 1955. Values for normal females, by this method, are approximately 10-15 mcg./24 hrs.

Urinary hormone excretion determinations were carried out as shown in Table I. Urinary levels of pituitary gonadotrophins were very high. Both 17-ketosteroid and 17-hydroxysteroid excretions were somewhat below normal levels, while urinary œstrogen (œstrone only) was in the range found in normal adult women, much above the level in males.

Because of the repeated hæmatemesis, and x-ray evidence of duodenal ulcer, laparotomy was performed. At operation, approximately two weeks after his last episode of bleeding, it was found that the ulcer was healed. No further procedure was carried out. The liver was noted to be normal in

gross appearance. A biopsy was not done. Testicular biopsy was not performed.

It was felt that the diagnosis of Klinefelter's syndrome was established on the basis of the clinical evidence of gynæcomastia, small testes and questionably palpable prostate, plus the laboratory evidence of chromatin-positive oral smears, "drumsticking" in the blood smears, and high urinary excretion of pituitary gonadotrophins. The multiple spider angiomata were unexplained.

DISCUSSION

The clinical syndrome of small testes, sparse hair growth and gynæcomastia is not found exclusively in pseudo-males. However, the finding of a high urinary excretion of pituitary gonadotrophins is very suggestive; and the observation, in two different tests, of sex chromatin positivity indicating the chromosomal femaleness of the patient is considered conclusive. Bunge and Bradbury[6] have pointed out that "the only known instances of positive chromatin test in 'males' have been in Klinefelter's syndrome."

The etiological factors involved, both in gynæcomastia and in spider angiomata, are not known with certainty. In 1947 Spankus and Grant[23] reported two cases of idiopathic gynæcomastia—both of which could be cases of Klinefelter's syndrome—and concluded that gynæcomastia is the result of a disturbed endocrine status usually related to an alteration of the normal androgen: œstrogen ratio. Rupp *et al.*,[21] in 1951, observed that the presence of gynæcomastia in liver disease was not correlated with the presence of high urinary œstrogen excretion. In 22 cases of gynæcomastia without demonstrable liver disease, increased urinary œstrogen values were recorded in only nine patients. Klinefelter, quoted by Bunge and Bradbury,[5] has made the suggestion that gynæcomastia results from the stimulation of glandular tissue by an abnormal steroid which does not inhibit the hypophyseal secretion of gonadotrophins.

Recently, Nelson[16] has suggested that in those individuals whose genetic sex is female there may be a "greater target-organ sensitivity, so that the breasts hypertrophy in response to normal or essentially normal levels of œstrogen". It is evident that no conclusion has been reached in this matter as yet.

Likewise, in regard to spider angiomata, research has led to no conclusion. Bean's suggestion that these lesions are the product of the stimulus of high levels of œstrogenic substances circulating in the blood for long periods seems the most plausible at the present time.

High levels of urinary œstrogen are unusual in Klinefelter's syndrome. Leach *et al.*[14] recommend estimation of urinary œstrogen as a measure of Leydig cell function in man, claiming that it is a more reliable index than 17-ketosteroid determination. Their reasoning is that 80% of the œstrogen excreted by normal males is formed in the testes, while only about one-half of the 17-ketosteroids are formed there. In the cases of Klinefelter's syndrome they report, urinary œstrogen excretion is in the range for normal males. And DeFelice,[8] in a review published in 1955, comments that "no changes in urinary œstrogens have been noted" in Klinefelter's syndrome.

Perhaps, in this patient with Klinefelter's syndrome, the presence of spider angiomata is due to an increased end-organ sensitivity to his circulating œstrogen, which is in the range of values found in normal females.

SUMMARY

A case of Klinefelter's syndrome is reported in a 32-year-old French Canadian. The diagnosis was established by the findings of gynæcomastia, small testes and questionably palpable prostate, with chromatin-positive oral smears, blood smears showing neutrophilic drumsticks, and increased urinary excretion of pituitary gonadotrophins.

The unusual feature of multiple spider angiomata in a patient with Klinefelter's syndrome is noted. Urinary œstrone excretion in the range expected for normal females was also found in this patient.

We would like to express our thanks to the following: Dr. K. L. Moore, Assistant Professor, Department of Anatomy, University of Manitoba, for reading the manuscript, and for his interpretation of the oral smears; Dr. J. P. Maclean, Director, Clinical Investigation Unit, St. Boniface Hospital, for his assistance in obtaining the endocrine assays, and for his general advice; Dr. H. H. Gunson, Research Fellow, Department of Pædiatrics, University of Manitoba, for his interpretation of the blood smears; Drs. J. C. Beck and E. H. Venning, Royal Victoria Hospital, Montreal, for performing the gonadotrophin assay; and Dr. J. Linford, Assistant Professor of Biochemistry, University of Manitoba, for performing the œstrogen assay.

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(A.G.R.) Department of Medicine,
Mall Medical Group,
Winnipeg, Manitoba.

COMBINED INTRAUTERINE AND EXTRAUTERINE PREGNANCY

R. H. GELB, M.B., Ch.B., M.R.C.O.G.,
Guelph, Ont.

COMBINED intrauterine and extrauterine pregnancy is uncommon, with an incidence of about 1 in 30,000 pregnancies. A review of the world literature[1, 4] reveals 466 documented cases of this condition. To these we would like to add two cases of our own, one of which must surely be almost unique.

No one likes to be deceived, and if we can prevent others from being lulled into a false or incomplete diagnosis as a result of our experience with these two cases, this report will be fully justified.

ETIOLOGY AND PATHOGENESIS

The term "combined pregnancy" implies that the pregnancies must coexist with live fetuses at the same time, and result from a single fertilization or two separate fertilizations within a relatively short period of time. It seems fairly certain that the large majority of these cases are twin pregnancies which originate from a single coitus and have separate sites of implantation, one of which is the uterine cavity.

Because it has never been shown that monozygotic twins can be partitioned and then choose different sites of implantation, it must be assumed that all combined pregnancies are the result of fertilization of two ova. It may further be postulated that these ova arise from two different follicles in one or both ovaries, or may even arise from the same follicle, as evidenced by the finding of a single corpus luteum at the time of operation.

Regardless of the time of ovulation or fertilization, one ovum proceeds normally through the Fallopian tube to the uterine cavity, while the other becomes arrested in its course for any one of a number of well-known causes. These postulates and facts do not, however, explain the first of our cases, where only one tube and one ovary were present, unless delayed implantation is assumed to have produced an ovum too large to pass down the Fallopian tube.

When the incidence of fraternal twins is correlated with that of ectopic gestations, the incidence of combined pregnancy works out at 1 in 30,000 gestations or 0.003%. If this figure is correct, either only a small number of cases are reported or many cases are not diagnosed. The finding of placental tissue in the uterine cavity is possibly taken as proof positive of the diagnosis of intrauterine pregnancy and the ectopic gestation is ignored or missed, hence the paucity of reports on such cases.

CASE 1.—Mrs. I.R., a 30-year-old married white woman, para 2, was seen in December 1957, complaining of severe lower abdominal pain, nausea and vomiting and some vaginal bleeding. Her last menstrual period had occurred on November 22, 1957. She stated that she was sure she had an ectopic pregnancy, as five years previously she had felt exactly the same symptoms and an operation had then revealed an ectopic gestation in the left Fallopian tube.

She was pale, apprehensive and complaining of constant lower abdominal pain. Her blood pressure was 116/70 mm. Hg, temperature 98.6° F., and pulse rate 100. The upper abdomen was tender but soft, with marked tenderness on suprapubic pressure. There was no rebound tenderness and no masses could be felt. On vaginal examination the uterus was found to be enlarged to the size of a 10-week pregnancy, and blood clot, with what appeared to be products of conception, could be seen protruding at the cervical os. She was transferred to hospital and curettage was performed. The specimen obtained was examined histologically and was found to be degenerating placental tissue. She apparently improved and was discharged from hospital. Ten days later she was again seen, complaining of severe pain in the right iliac fossa, nausea, vomiting and a moderate amount of vaginal spotting. She appeared pale, sick and anxious. Her temperature was 99° F., pulse rate 110 and B.P. 110/70 mm. Hg. The entire abdomen was tender to palpation, particularly suprapubically. Rebound tenderness was present throughout the lower abdomen. No masses could be felt. Vaginal examination revealed uterine enlargement to the size of an eight-week pregnancy. There was marked excitation pain and exquisite tenderness in the left adnexal region. She was again hospitalized with a tentative diagnosis of ectopic gestation or post-abortal pelvic inflammatory disease. The finding of chorionic villi in the tissue removed from the uterus at the previous operation was presumed to negate the first diagnosis, and she was given broad-spectrum antibiotic therapy. After 48 hours there was some improvement but vomiting and pain persisted. After a further 72 hours, immediately after a fairly vigorous vaginal examination, she went into a state of extreme shock with signs indicative of some intra-abdominal catastrophe. An emergency laparotomy revealed a distended right Fallopian tube surrounded by organizing blood clot, adherent to the posterior uterine wall, matted omentum and small bowel. The hæmatocœle was removed and a right salpingectomy performed. The left adnexa and ovary were absent as a result of her operation five years previously. The pathologist reported an ectopic gestation in the ampullary portion of the Fallopian tube. The postoperative course was uneventful and the patient left hospital on the 10th postoperative day in good condition.

CASE 2.—Mrs. M.M., a 30-year-old white woman, para 6, was admitted to hospital on March 10, 1958, with a history of constant lower abdominal pain and vaginal bleeding. Her last menstrual period had started on January 16, 1958. The diagnosis of inevitable abortion was confirmed when the cervical os was found to be 2 cm. dilated, clots and fresh blood issuing from it. Histologically confirmed products of conception were obtained from a curettage. The patient remained in hospital but did not improve; 48 hours later, she complained of severe lower abdominal pain, associated with nausea and vomiting. A bloodstained, foul vaginal discharge was present.

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The patient was an obese, sick woman, grunting with pain. Her pulse rate was 100, temperature 101.3° F., and B.P. 104/74 mm. Hg. The abdomen was distended and there was marked guarding and rigidity with well-marked rebound tenderness over the whole lower abdomen. Vaginal examination revealed a tender, bulging mass occupying the posterior fornix and pushing the cervix up under the symphysis pubis. The uterine size and the state of the adnexa could not be determined because of the extreme tenderness. A tentative diagnosis of pelvic abscess with pelvic peritonitis was made, and she was given suitable antibiotic therapy for 24 hours. A posterior colpotomy was then performed, and a large quantity of foul-smelling blood clot was evacuated from the pouch of Douglas. Laparotomy revealed a mass, surrounded by blood clot, in the right Fallopian tube, to which was adherent small bowel and omentum, and this in turn was attached to the posterior uterine wall. The mass was completely excised and was found to be an ectopic gestation containing an embryo approximately 2 cm. in length. This was surrounded by hæmatoma, the ovary forming part of the wall of the hæmatoma. After operation there was some improvement, but intermittent spikes of temperature were still present. This was thought to be due to thrombosis of a superficial vein in the right thigh. Four days later a copious discharge of pus from the abdominal wound appeared; culture revealed *B. coli* sensitive only to chloramphenicol. Two days later the patient complained of severe right chest pain on breathing. Examination showed signs of an effusion at the right base; this was confirmed by radiography. With the improvement in the chest condition the patient complained of pain in the right costal region. There was marked tenderness in this area, and radiography revealed elevation of the diaphragm on the right. This, together with the spikes of nocturnal pyrexia, was taken as indicative of a subdiaphragmatic abscess. Suitable treatment was instituted and the patient was finally discharged as fit and well on May 9, 1958, after a total stay in hospital of 57 days.

DISCUSSION

The striking fact which emerges on reviewing the series of cases in the world literature, including our own, is the rareness with which the correct diagnosis was made. The presence of a co-existing pregnancy is frequently overlooked even after circumstances have removed the first. In 71 cases reviewed by Winer, Berman and Fields[4] the correct diagnosis was made seven times.

Diagnosis

The condition of combined pregnancy should be considered in the differential diagnosis of twins, ectopic gestation and abortion whenever conflicting signs and symptoms are present. Cautious observation should be the pattern of management. The finding of an intrauterine pregnancy does not exclude the possibility of a co-existing extrauterine pregnancy; conversely, the finding of an ectopic gestation should not lead the attendant to discard a previously made diagnosis of intrauterine pregnancy. Unilateral pain in threatened abortion should always be viewed with suspicion, and the presence of a unilateral swelling coexistent with an intrauterine pregnancy should suggest the possibility of an ovarian cyst or an ectopic gestation. Careful bimanual examination before curettage, together with the judicious employment of colpotomy, culdoscopy and radiography when indicated, may aid in the diagnosis of a possible ectopic gestation. Often the finding of placental tissue in the uterine cavity is thought to confirm the diagnosis, and further search is obviated. Similarly when the signs and symptoms clearly point to a diagnosis of ectopic pregnancy, the slightly enlarged uterus is mistaken for the consensual hypertrophy and an intrauterine pregnancy thereby overlooked.

Treatment

Treatment of the ectopic gestation is surgical whenever it is recognized, regardless of the presence of an intrauterine gestation. In cases in which salpingectomy is performed early, postoperative care should be directed towards maintaining the intrauterine gestation. If examination before laparotomy reveals a closed cervix, minimal bleeding and the presence of a slightly enlarged and soft uterus, the surgeon should consider the possibility of disturbing an intact intrauterine pregnancy. Should the cervix show partial dilatation or bleeding be brisk, evacuation of the uterus at this time would be deemed correct treatment.

Prognosis

Past reviews have shown that the prognosis has been better for the mother where the initial symptoms were caused by the ectopic gestation, even though the intrauterine pregnancy was overlooked, since the more dangerous element of the condition was removed. In the cases where the ectopic gestation remained undiagnosed, although no deaths were reported, the period of morbidity was extended and the amount of residual permanent damage, although difficult to estimate, must surely have been profound. With the advent of improved surgical and diagnostic technique, the ready accessibility of blood, and the use of antibiotics, maternal mortality has dropped to less than 1%. The maternal morbidity, however, remains high, especially in cases in which the ectopic pregnancy is overlooked. This is amply demonstrated by our second case.

It has been shown that the large majority of combined pregnancies do not continue beyond the first trimester. When both pregnancies do continue beyond that point, a percentage may result in viable births. The continuance of the ectopic pregnancy to term under these conditions may be explained on the basis of a better blood supply to the pelvis in conjunction with the intrauterine pregnancy. The survival rate of the extrauterine fetus in these cases has been given as high

as 10%. Of these, however, no more than half survive the first week of neonatal life.

SUMMARY

Combined pregnancy has been recorded in the world literature on 466 occasions. Two further cases are reported.

Some aspects of etiology and pathogenesis are discussed. A correct diagnosis has rarely been made in the recorded cases; the difficulty of diagnosis of combined pregnancy is recognized. Failure of recognition can lead to increased maternal morbidity and profound permanent pelvic damage.

Treatment of combined pregnancy is usually surgical. Management of the uterine pregnancy is conservative, unless abortion is inevitable or spontaneous.

Most combined pregnancies terminate in the first trimester. If the condition continues beyond this point, viable infants may be delivered.

The diagnosis can be made more often if the possibility of combined intrauterine and extrauterine pregnancy is borne in mind. In the presence of conflicting signs and symptoms, errors may be avoided by the employment of available diagnostic procedures and the use of judicious management.

Sincere thanks are due to the following for their help and co-operation: Dr. F. J. Kirvan, Dr. S. Witt, Dr. E. L. Barton, Sister M. Audry and the staff of St. Joseph's Hospital, Guelph, Ontario.

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109 Norfolk St.,
Guelph, Ont.

METASTASIZING CARCINOID (WITH A CASE REPORT OF THE CARCINOID SYNDROME)

E. J. BEATON, M.D.,* *Hamilton, Ont.*

CARCINOID TUMOURS were first described accurately by Lubarsch in 1888. Although Oberndorfer designated them as "carcinoid" in 1907, they are now accepted as slowly growing carcinomas which may occur anywhere in the gastro-intestinal tract, and rarely in the gall-bladder and in teratomas of the ovary and testicle. Combined surgical and autopsy incidence is approximately 0.1%. Two cases out of three occur in the appendix, mostly in young females. Of the remainder, two-thirds occur in the small bowel of middle-aged people. Recent reports indicate an increase in the incidence of carcinoid of the rectum, which is usually detected as a submucous nodule on the anterior rectal wall.

*Resident in Surgery, Hamilton General Hospital.

Since 1930 it has been appreciated that extra-appendicular carcinoids metastasize frequently. Primary lesions in small bowel may metastasize in 75% of cases (cf. large bowel 50%, stomach 20%). The rarity of metastases from a primary in the appendix (about 1%) may be due to its anatomic location giving rise to early symptoms in young people with small appendices. One must remember, too, that appendectomy remains the commonest abdominal operation, it is performed commonly in young people, and it provides a very large number of surgical specimens for examination. Carcinoid metastases occur in regional lymph nodes, liver and serosa, and terminally in lung and other distant organs.

The pathology, gross and microscopic, will be encountered in the case report below. Suffice it to say here that the histochemical tests for these tumours are many, and merely indicate that the cell vacuoles contain a mixture of neutral fats, cholesterol esters and lecithin. As some carcinoids are not argentophilic, the most specific of these tests is probably the indophenol reaction.

Seventy years ago Lubarsch asserted that these tumours were carcinomata arising from the crypts of Lieberkühn. Since then many genetic theories have "passed under the bridge" until at present the tumours are again regarded as carcinomata arising from the Kultchitsky cells which are found in the epithelium of the gastro-intestinal and biliary tracts and which occur most commonly in the crypts of Lieberkühn. It is well to realize that over the years these K-cells have acquired many and often confusing synonyms which include: argentaffin, chromo-argentaffin, entero-chromaffin, chromaffin, chromaphil, gelbe Zellen, Nicolas and Schmidt cells. These naturally occurring cells and carcinoid cells have been shown to have identical sites and staining reactions, and both secrete 5-hydroxytryptamine (5-HT) into the blood stream.

In 1949, Rapport showed that serotonin in the blood was 5-HT. By 1952, Erspamer had isolated enteramine from the K-cells and identified it as 5-HT. A theory was put forth that the amino acid tryptophane is converted by a decarboxylase enzyme system in the K-cells to 5-HT, which is then secreted in the blood stream and taken up mostly by platelets. The portal and hepatic veins then carry this serotonin to the right heart. While passing through the lungs it is converted by monamine oxidase to 5-hydroxyindole acetic acid (5-HIAA), a completely innocuous substance which is excreted in the urine.

5-Hydroxytryptophane can enter the brain and be converted by the decarboxylase enzyme there into serotonin, but the latter cannot enter the brain from the peripheral circulation except when present in large amounts. Monamine oxidase, present in large amounts in the brain, inactivates serotonin to 5-HIAA. Lysergic acid diethylamide (LSD), which produces mental changes in man, antagonizes the central effect of serotonin, and Brom LSD an-

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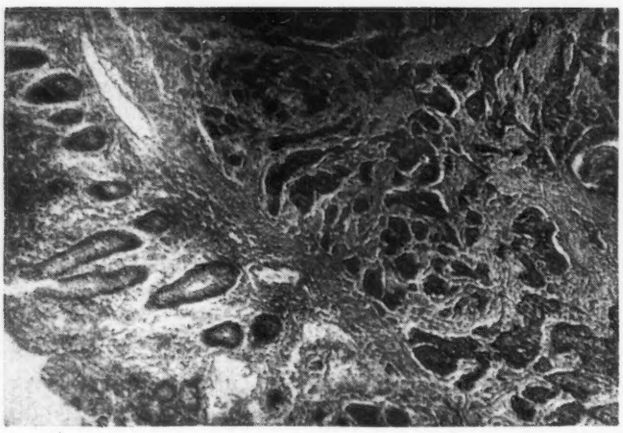

Fig. 1.—Primary carcinoid of ileum, 1940, showing submucosal invasion by clumps and nests of cells. × 10.

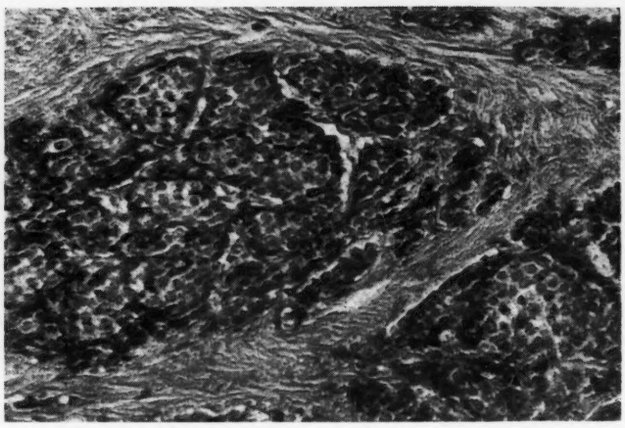

Fig. 2.—Higher magnification of Fig. 1 showing central pale cells with darker staining cells at the periphery.

tagonizes the smooth muscle effect of serotonin. The neurologic and psychiatric aspects of serotonin have been subjected to close scrutiny of late, but for practical purposes require no further consideration in our present discussion.

Cassidy, in 1931, reported a case of flushing, cyanosis, pulmonary stenosis, diarrhœa, abdominal pain and a palpable knobby liver. In 1952, Biorck associated this syndrome with metastasizing carcinoid. In 1953, Lembeck showed that some carcinoids contain large amounts of 5-HT with elevated levels of 5-HIAA in the urine. Thus was evolved the carcinoid syndrome with the following triad of features: (1) carcinoid with metastases; (2) episodes of flushing, with telangiectases of the skin; (3) sclerosis of the tricuspid and pulmonary valves with tricuspid insufficiency and pulmonary stenosis. Cardiac signs are late and require cardiac catheterization and angiocardiography for detection, as radiographs and ECG may be normal. About 40 cases of carcinoid syndrome have been reported, but more probably exist, with only one or two of the features present. Associated symptoms include diarrhœa, abdominal pain, dyspnœa, arthritis, œdema and pellagra. The latter may be rectified by increasing the tryptophane intake to 500 mg. daily. Pharmacologically 5-HT is quite active, with emphasis on smooth muscle contraction in the early phase, and flushing, cyanosis and cardiac changes later, due to a prolonged high level of blood serotonin.

The diagnosis of metastasizing carcinoid is made easy by the qualitative and quantitative tests available for determining the level of urinary 5-HIAA. Prognosis is guarded but not poor, considering that some patients live for several years in reasonable health.

Treatment is ineffectual when the liver is full of metastases. Surgery may provide relief by removal of the primary lesion, and occasionally by removal of the metastases, but the operative risk is considerable. Radioactive gold has been used in the few who develop ascites, with temporary relief. Antihistaminics have helped only those cases with an associated high blood-histamine level. Radiotherapy is valueless. Potent antagonists, such as Brom LSD, chlorpromazine and dibenylene, have not as yet given conclusive results.

The following case report of the carcinoid syndrome will amplify certain pathological and clinical aspects of the brief review outlined above.

Clinical history.—The patient, a farmer now 61 years of age, was admitted to hospital in June 1940 with crampy, central abdominal pain, and recent constipation. Physical findings were essentially normal. Symptoms abated after a successful enema, and a barium series was normal.

Three months later he was readmitted in acute distress with an interim history of similar episodes and a weight loss of 25 lb. Laparotomy revealed a small constricting tumour of terminal ileum approximately 30 cm. from the ileocæcal valve. The ileum proximal to the tumour was thickened and dilated; distally it was thin-walled and collapsed. The adjacent mesentery contained a few palpable, firm glands but the liver appeared normal. A wide wedge resection of terminal ileum and mesentery was performed, with side-to-side anastomosis. Convalescence was uneventful and he left hospital on the 19th postoperative day.

Pathological examination.—The specimen consisted of a portion of ileum measuring 50 cm. in length attached to a wedge of mesentery measuring 15 cm. at the apex. On opening the lumen a sessile tumour with central ulceration was found in the mid-point of the length of ileum, corresponding to the site of serosal puckering noted at operation. The tumour measured 1.5 cm. in diameter and projected 1 cm. into the lumen. Cut surface was firm and pale yellow. Four mesenteric glands, measuring up to 1.5 cm. in diameter, were also firm and pale yellow on cut surface.

Microscopically the mucosa over the central portion of the tumour mass was completely ulcerated. The submucosa was occupied by irregular nests of cells infiltrating the muscle coat. These cells were small, round and clear-staining with eccentrically placed nuclei. Lymph glands displayed a similar cellular pattern.

Diagnosis.—Carcinoid tumour of ileum with metastases to regional lymph glands.[14]

Follow-up.—For the next 15 years this patient was under the close observation of his family physician.

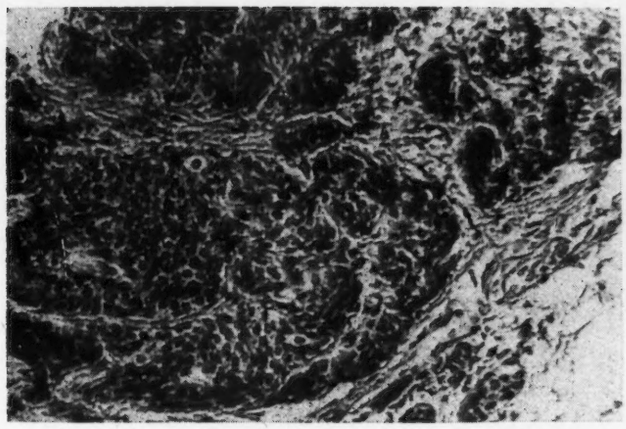

Fig. 3.—Metastatic carcinoid of ileum, 1957, showing smaller, darker, more active-looking cells. The nest-formation is still apparent.

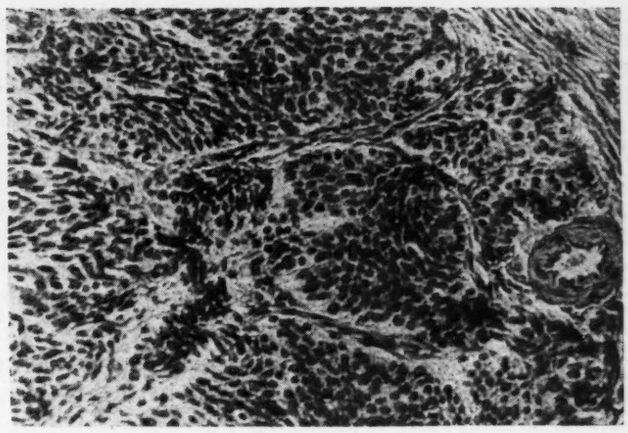

Fig. 4.—Metastatic carcinoid of peritoneum, 1957, quite similar to that in Fig. 3.

During the first few years of this period, he continued to work on his farm and remained well apart from sporadic bouts of crampy abdominal pains with distension and vomiting. He began to have 1-2 loose stools daily. In 1944, while chasing some wayward cows across the pasture, he "blacked out", sustaining a head injury with subsequent disorientation for two days. No satisfactory cause could be found for the initial blackout and it was not repeated. During the next few years the symptoms of pain became dissociated into two components: abdominal pain which shifted more to the right upper quadrant, and right "hip and knee" pain which was attributed to long-standing osteoarthritis of the right hip. A barium meal was normal. By December 1955, abdominal pain, distension and vomiting became severe enough to necessitate readmission to hospital. Radiograph of the abdomen showed a dilated segment of small bowel. Symptoms and signs subsided within 24 hours on a regimen of intravenous fluids and gastro-intestinal suction. A diagnosis was made of subacute bowel obstruction due to adhesions. This episode was followed by similar attacks of increasing severity with anorexia, weight loss and 3-4 loose stools daily. No respiratory or genito-urinary complaints were noted.

In April 1956, an obturator neurectomy was performed successfully for the relief of the pain in his right hip. Following this, pain in the right upper quadrant became such a prominent factor that a cholecystogram was done, and reported normal. Barium enema was normal except for one fixed pelvic loop of bowel.

During the summer of 1956, a curious flushing of the skin appeared, associated with vertigo, faintness and hypotension. Symptoms progressed in severity and the patient was readmitted to hospital on December 26. Examination revealed a well developed, fairly well nourished man of 60 years with a deep pinkish-red blush to his face, hands and forearms. Clinically the cardiovascular system was intact; the blood pressure was 128/88 mm. Hg. Lower abdominal quadrants were distended, with equivocal rebound tenderness; bowel sounds were present, however, and the patient was placed on a soft diet, which he tolerated well. Several senile angiomas lay scattered over the trunk. An upper gastro-intestinal series showed normal œsophagus, stomach and duodenum, with slight hold-up of barium through a 35-cm. fixed segment of small bowel in the midline just anterior to sacrum. A similar finding was noted just medial to the ascending colon. There was no delay from small to large bowel, the barium reaching cæcum in 1½ hours. Routine urinalysis and blood work were normal.

On January 7, 1957, a right transverse rectus-cutting incision was made. The terminal ileum was bound down in several places to the posterior wall by hard, tumour-like tissue. Frozen sections revealed carcinoid tumour. The upper surface of liver was studded with metastases. A portion of terminal ileum was resected with end-to-end anastomosis. Pulse and blood pressure remained normal throughout the operation. Diarrhœa complicated the postoperative period but did not prevent his going home on the 13th postoperative day.

Pathological examination.—The main specimen consisted of three loops of small bowel matted together in continuity by reddish fibrous-like adhesions. The bowel measured 45 cm. in length. The serosa and mesentery were studded with several white, opaque plaques and nodules measuring about 0.5 cm. in diameter. The mucosa was intact. The irregular, rubbery fragment for frozen section measured about 1.5 cm. in diameter and on cut surface was a mottled white and yellow.

Microscopically, nests of carcinoid cells were found invading bowel wall, mesentery and posterior parietal wall. Mitoses were frequent, and the cytoplasm was filled with coarse, granular chromatin granules. Chronic inflammatory cells were noted in the stroma.

Diagnosis.—Metastasizing carcinoid tumour (ileum, peritoneum, liver).

Recently, while driving his car, the patient sustained another blackout and required sutures to a laceration of the forehead. Since then he has felt weaker, with increasing anorexia and a further weight loss of 25 lb. over the past 15 months. One attack of renal colic was noted.

His cardiovascular system remains intact clinically, with pulse 64, B.P. 136/84, heart sounds normal, and no jugular venous filling, dyspnœa on effort or peripheral œdema. ECG was reported normal. A colorimetric test of urine showed a high level of 5-HIAA.[11]

DISCUSSION

The pharmacological effects of serotonin reach a pathological degree in the carcinoid syndrome to produce the clinical manifestations which include flushing, diarrhœa, dyspnœa, and abdominal pain.

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For the past two years this patient has complained of curious pinkish-red flushes which occur with meals, and are associated with anorexia, weight loss, anxiety, post-prandial weakness and vertigo. The onset of each chromatic episode is ushered in by a constricting, hot feeling in the cheeks, spreading to the forehead, neck, hands, forearms and thighs. The average duration of this irregular eruption is about one minute, the longest attack lasting five minutes. Weakness often necessitates a half-hour rest lying down.

Ingestion of brandy effects a sudden accentuation of the flush within 30 seconds to all areas mentioned, producing an intense, burning pain in the face especially. This is the so-called "brandy" flush. It is interesting that his flushing has decreased from three times a day to once a day after breakfast. Loose, watery, blood-streaked stools which occurred two and three times daily in 1945 have increased to four and five times daily, with tenesmus. Symptomatic treatment and a soft diet have somewhat curtailed the severity of this complaint. Dyspnœa, which is most marked in the mornings, is not asthmatic in type nor is it associated with any audible heart murmurs, angina or œdema. It may be a transient bronchiolar spasm associated with the flush. Pain of a colicky nature may be attributed to the smooth muscle contraction by serotonin, producing increased bowel motility and a recent attack of renal colic. The steady, boring pain in his right upper quadrant, however, is due to a knobby, metastatic liver one hand's breadth below the costal margin in the right mid-clavicular line. Central effects of serotonin are possible,[4] and perhaps account for the two episodes of unexplained blackout.

The longevity of this patient with carcinoid metastases may be due to the excision of the primary lesion 18 years ago, the circulating serotonin thus being deprived of its most potent source of supply. On the other hand, it has been shown that some metastases can supply more precursor substance (5-hydroxytryptophane) than does the primary tumour. If this latter possibility should apply to the present case, it must be postulated that some hormonal antagonist may be elaborated *in situ* to create an auto-balance. There are several known anti-serotonin metabolites which exert peripheral and central effect, e.g. Brom LSD and LSD.

Primary carcinoids can ulcerate. They do not all remain as a submucosal tumour.

SUMMARY

A brief review of metastasizing carcinoid has been presented, with a case reported in which a patient has gone on to develop the carcinoid syndrome over a period of 18 years.

I wish to thank Miss J. Ashley of the Photography Department of the Hamilton General Hospital, and Drs. F. B. Hamilton, C. L. Bates and E. N. Ballantyne, for their kind co-operation.

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VESICAL FIBRIN STONE*

N. C. CARRUTHERS, M.D., *Toronto*

IN 1818, Marcet first described the presence of fibrin stones in the urinary tract. Since that time, 38 cases have appeared in the literature. Of this number, 17 were confined to the bladder. The eighteenth case of the latter is presented here.

The term fibrin stone is only one of a variety of names applied to these soft, free bodies found in the urinary tract. Others include albumin stone, bacterial stone, colloid stone, fibrinoma, and sarcoidopseudolith. The last of these is probably the most descriptive and means "soft, false stone". This term was coined by Lich and Maurer, who reviewed the literature in 1955.

These vesical "foreign bodies" are usually described as fleshy, spongy, non-calcified, and unattached within the bladder lumen.

The etiology of the condition is not known. All previous cases have been associated with persistent urinary tract infection. Those cases confined to the bladder have shown lower urinary tract obstruction, usually of recent onset. At least three cases have followed transurethral resection of prostate or tumour.

A 77-year-old white man was admitted in July 1958, for investigation of gross, painless hæmaturia of recent onset. In 1948, a malignant papilloma of the bladder had been excised transurethrally. Follow-up cystoscopic examinations were done regularly until 1952, when they were discontinued. No recurrences had been seen. No urinary difficulties had occurred in the interim until this admission.

Examination on admission revealed no significant abnormalities except for moderate obesity. The blood pressure was 140/80 mm. Hg. and the heart and chest were clinically normal.

Urinalysis on admission showed a specific gravity of 1026, albumin 3+, sugar 4+, acetone 2+, and 5-10 white cells per high power field. The fasting blood sugar was 210 mg. % and the postcibal blood sugar

*From the Department of Urology, Sunnybrook Hospital, Toronto.

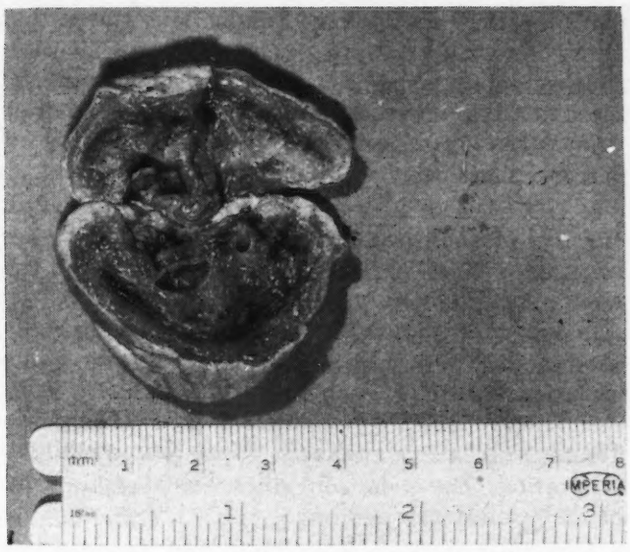

Fig. 1.—Showing gelatinous, cystic, laminated appearance of the cut surface of the foreign body.

380 mg. %. Urine culture revealed *Bacterium coli* resistant to all tested antibiotics.

Intravenous pyelography showed no significant abnormalities. No calculi were seen in the urinary tract.

At cystoscopy, a papillary tumour was seen on the bladder floor. A surrounding zone of œdema was noted. In the dome of the bladder, at the site of the air bubble, a large, greyish-white stone was seen. Because it could not be dislodged into the dependent part of the bladder, it was felt that this stone was adherent to a tumour mass at the bladder dome. Because of the size of the stone and the associated tumour, the decision was made to approach both suprapubically. The diabetic condition was easily controlled preoperatively by diet alone.

At operation, no evidence of tumour was found at the dome of the bladder, and the so-called stone was seen lying free on the floor of the bladder. It had the consistency of a marine sponge, was greyish-white and elliptical, and measured 4 cm. in longest diameter. On cut section, this fibrinoid structure was laminated, cystic, and fleshy-pink in colour (Fig. 1). The bladder tumour was resected with the loop electrode and the base thoroughly coagulated.

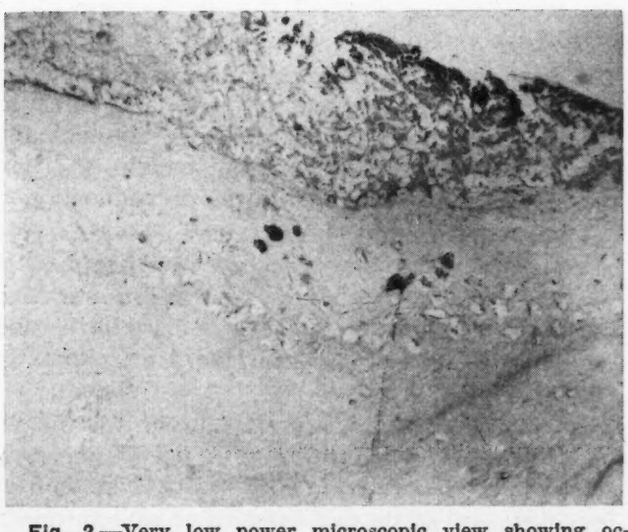

Fig. 2.—Very low power microscopic view showing occasional clumps of bacteria in the amorphous pseudolith.

Microscopic examination of the object removed from the bladder showed an amorphous structure containing clumps of bacteria (Fig. 2). The micro-organism was not identified bacteriologically.

Postoperatively, the course was smooth for 24 hours. Then, the patient developed a staphylococcal pneumonia and staphylococcal enteritis. The clinical course was progressively downhill and death ensued on the sixth postoperative day.

DISCUSSION

Vesical fibrin stone or sarcoidopseudolith is a relatively rare condition of unknown etiology. There seems little doubt that micro-organisms play some role in formation of these stones because bacteria are routinely found clumped within the laminated architecture. The organism has not been identified in all instances, but staphylococci, streptococci, *Ps. pyocyanea*, and *Bact. coli* have been isolated. Infection would, of course, be predisposed to by lower urinary tract obstruction, which has been present in all recorded cases. Ikoma has been able to produce similar deposits *in vitro* using bacteria obtained from one of his patients and blood. The relationship between fibrin stone and transurethral resection of tissue raises the possibility of retention of a fragment of resected tissue or blood clot, which might then act as a nucleus for the deposition of amorphous fibrin material and consequent formation of a fibrin stone. Such speculation could not be proven in this case because no tissue could be recognized by microscopy.

The urologist is apt to be misled by seeing, at cystoscopy, an obvious "stone" in the bladder (in this case a large one) which is in the superior segment of the bladder lumen. It is immediately thought that the "stone" has formed overlying a tumour of the vault of the bladder. Confusion is added by failure of the radiologist to demonstrate any stone in pyelographic films. Filling defects may be seen, however. These features should suggest the presence of a pseudolith, and attempts may then be made to aspirate the mass through a resectoscope sheath or other instrument with a suitable lumen. In our case, the pseudolith was of the consistency of marine sponge and would doubtless have been easily removable by this means. Suprapubic cystotomy was decided upon because of the associated bladder tumour and the suspicion that one existed beneath the stone. In any event, the "stone" would have been considered too large for endoscopic removal.

SUMMARY

The eighteenth case of vesical fibrin stone or sarcoidopseudolith has been presented. The diagnosis may be considered when an apparent stone is seen at cystoscopy but not demonstrated by x-ray in spite of an apparent calcific covering. Such pseudoliths are of soft consistency and could probably be aspirated from the bladder transurethrally. They are associated with urinary tract infection and lower urinary tract

obstruction in all recorded cases. Our case had the additional factor of the presence of a malignant bladder tumour.

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Special Article

THE FAMILY DOCTOR AND THE HANDICAPPED CHILD AND YOUNG ADULT*

DONALD PATERSON, M.D., F.R.C.P.[Lond.& C.], *Vancouver, B.C.*

THE INVITATION to speak at this celebration allows me to bring before you a matter of the greatest importance to the medical profession and the citizens of Canada. I ask you this question — are we doing our full share in helping handicapped children?

EXTENT OF THE PROBLEM

I have attempted to compile the number of handicapped persons in Manitoba. It would appear that with a population of approximately 900,000 there will be at least one person per hundred or 9000 mentally retarded in the province. Of these, three-quarters will be in the group with an intelligence quotient down to 50, which will allow them to be educated in special classes in the ordinary public schools, and with proper care and attention they can be taught to be self-supporting. The next group make up 20% of the total and they have an intelligence quotient of from 25 to 50, and these can be taught to look after themselves and perform certain tasks under supervision but will not be self-supporting. Finally, there are those with an intelligence quotient under 25 who make up 5% of the whole, and these will need institutional treatment sooner or later. New cases are being added to this total each year, and the numbers in the total population will inevitably rise with the greatly lowered mortality rate due to the advent of antibiotics.

It is estimated by Phelps that there are 7 babies with cerebral palsy born yearly for each 100,000 of the population. In Manitoba this would represent 63 cases per year. It is also estimated that 50% of these can be helped to become useful citizens and earn their own living. Finally, it is stated that about one-third of all such children have an average intelligence. No estimate is made of the total number of cases in any community, but it will clearly run into something in the region of one thousand cases in your province.

Lord Cohen of Birkenhead, writing in the *British Medical Journal* recently, has estimated the number of epileptics as at least 3 per thousand of the population, which would give a total of 2700 sufferers. Fortunately, the majority are mentally normal and are educable, and can with some understanding by the public and industry earn their living and live productive lives. There are great problems connected with the remaining proportion, however, and these need your help in their solution.

Various estimates have been put forward for the number of deaf and hard-of-hearing. These range all the way from 4 to 1% of the population. Even if we take the lower figure, you will be confronted with 9000 persons who have varying degrees of this most serious handicap.

Turning to the blind, or those with some degree of sight loss, we have no accurate way of estimating their numbers. One can say that in a survey of recent years undertaken in B.C. school children, we were surprised at the large number found among the 20,000 handicapped children discovered. There were some 8000 children who had some loss of sight due to squint or refractive errors or worse. One can easily imagine the high proportion of such children masquerading as inattentive or disinterested pupils who need your help. That efficient organization, the C.N.I.B., deals with the more serious cases but there remain many less serious but handicapped, which you must deal with.

Among the 22,000 infants born each year in Manitoba you will have approximately 25 cases of hare lip and cleft palate, 18 cases of congenital heart disease, and 36 children with club feet. Some of these children do not survive, but the majority do, and the numbers will steadily increase along with the population.

A new group has been produced of recent years by our modern method of living. I refer to children suffering from accidents, burns, and poisoning. You will be giving thought to campaigns to educate the public in prevention.

I have said nothing about children with severe dental caries, and the education of the public in the benefits of fluoridation. I have not estimated the numbers of those suffering from arthritis and rheumatism, tuberculosis and the after effects of poliomyelitis.

In summary, then, we are faced with the following. There are in Manitoba at least 9000 mentally retarded, 1000 cerebral palsy cases, 2700 epileptics, 9000 deaf or hard-of-hearing, an undetermined number of blind or partially blind, a steadily in-

*Presented at the 50th anniversary meeting of the Manitoba Medical Association, Winnipeg, Man., October 1958.

creasing number of infants born with congenital malformations or damage at birth as well as numbers of persons damaged by burns, accidents, poisonings, arthritis and tuberculosis.

I am sure sufficient has been said to arouse your interest in this very real and growing problem.

There is a tendency for the practice of medicine to alter over the years. The advent of antibiotics has completely changed the outlook. Acute infections will tend to grow fewer in number and to be treated early and efficiently, often without help of the family doctor at all. Where then lies the field of the future for the family doctor? I believe that in the next twenty years, a large part of your practice will be made up of the medical rehabilitation of the handicapped, and it is to this side of medicine that I wish to direct your attention today.

ROLE OF THE FAMILY DOCTOR

The medical profession from its training and outlook should be the logical champion of the handicapped. To do this properly, however, the family doctor will require to work on the following lines.

First: He will require a complete diagnostic and long-term treatment service made available to his patient. This is especially necessary where multiple disabilities are present. The team approach in each type of disability is the modern way of tackling the problem. When possible, he should be present at such team conferences or at least the summing up of each child's case and have a full report in writing which he can explain in detail to the parents.

Second: With the information before him he will be able to answer questions as to the child's future, and help the parents to plan it in as realistic a manner as possible.

Third: He must encourage the parents to carry out the treatment suggested, and not allow them to adopt the attitude so often taken that the child will grow out of the trouble by the age of seven years or fourteen or so on. Some parents hide the child away and are prone to suffer from self-accusation or self-pity. The family doctor must step into the picture and encourage the parents to face the situation, if they are to give their child the chance he deserves.

Fourth: When the child attends school, much medical interpreting may require to be done to the school authorities by the family doctor. He must be constantly on the lookout for emotional difficulties, and take steps himself or see that the parents seek expert advice to prevent these difficulties developing. Overprotection must be guarded against. Expecting too much from the child may precipitate emotional disturbances.

Fifth: When the child is preparing to leave school, and the question of the choice of some training for future work arises, the family doctor must take an active part. Along with the school principal, the school nurse, the local medical officer of health, the national employment officer and sometimes the social service representative and parents, he may take part in a round table conference. With such a group, all aspects of the child's physical, mental, and emotional make-up may be considered, and some suitable training and employment planned. It is here that the family doctor, with the whole medical background of such a child known to him, can be of the greatest assistance in interpreting the child's limitations to the rest of the team.

Before special facilities for the diagnosis and continuing treatment of the various handicaps can be organized, it is necessary to know the number of children involved, the nature of their disability, and their ages, where they live, whether they are under treatment already, and so on. This involves the establishment of a registry for handicapped children and young adults. Registration is best done on a voluntary basis. In the course of the collection of such statistics by a registry over the years, a constant flow of hitherto unknown cases will be discovered, and facilities for helping them will be instituted.

When any doctor thinks back into his own practice, he will at once recall several children or young adults who have a severe handicap for which little or no treatment may at present be available. If each of you, however, would register your cases, the number would run into hundreds or even thousands; the real problem would then become evident and steps could be taken to set it right.

REGISTRATION OF CASES

A registry for handicapped children and young adults could best be under the dual control of the Division of Vital Statistics and the Public Health Department. The statistics to be of any use must be accurate and compiled in such a way that they are meaningful to the medical profession. For instance, there should be no duplication. The completeness of the figures can only be achieved by tapping all sources, such as treatment centres, in-patient and out-patient departments, all special clinics for special handicaps, and public health and welfare staffs in the field. Since by far the largest number of cases are under the care of the private doctor, his co-operation is essential. Using such figures, even if incomplete, to point to deficiencies in services for the handicapped is a necessary function of a registry. To be of maximum use, a registry should record all cases of all disabilities in the province and not just those cases which, owing to financial shortage, require special help and come under special notice. Only in this way will the incidence of such disabilities be known, so that steps can be taken to prevent them where

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DEPARTMENT OF HEALTH AND WELFARE, HEALTH BRANCH

REGISTRY FOR HANDICAPPED CHILDREN
828 W. 10th Ave., Vancouver 9, B.C.

Surname (please print)..... Christian Names..... Date of Birth.....

Address..... Sex: Male ☐ Female ☐

Name of Parents or Guardian..... No. of children in family.....

DIAGNOSIS: (Disabilities) DEGREE OF DISABILITY: Slight ☐ Moderate ☐ Severe ☐

.....

Is there any degree of Mental Retardation No ☐ Yes ☐ I.Q.....

Does this child because of disability require any of the following: Check items which apply.

1. Mental Investigation and/or Treatment ☐
2. Physical Rehabilitation ☐
3. Prolonged Institutional Care—Physical ☐
4. Institutional Care—Mental ☐
5. Special Educational Facilities ☐
6. Vocational Training ☐

NAME, POSITION, ADDRESS OF PERSON REGISTERING:—

Date:

ARE YOU REGISTERING THIS CASE FOR:—Statistics only ☐ Advice from Registry ☐ Active Follow-up ☐ If advice or follow-up, please complete rest of card.

Is family eligible for:—	Names of Hospitals or Travelling Clinics attended with dates.	Occupation of Father and/or Mother:
Hospital Outpatient Service ☐	.....	
Social Assistance ☐	.....	
Indian Health Services ☐		

Name and Address of Family Physician

With the exception of Vancouver, please return all cards through the Local Health Unit Director

Fig. 1

possible and to lay the foundations for future research.

The Public Health Department could use their facilities to gather these statistics and act as a link between the registry, the medical profession, and the public. In this way there will be no clash of interests, or fear of unethical communication by the registry to the doctor's patient. A registry should communicate to no one but the medical profession. It is also necessary for the registry to have complete support and confidence of the medical profession, which could be facilitated by appointing an advisory medical panel who could be consulted from time to time regarding policy.

What sort of case should be registered? The family doctor must say to himself, when faced by a child suffering from either a congenital or an acquired handicap – is this likely to make it difficult for this child to obtain his education or to earn his livelihood later in life? If so, that is a child who should be registered. Sufficient details should be recorded on the registration form for another doctor to have a good idea of the nature and extent of the disability (severe, moderate, slight). The record is more helpful if it includes the intelligence quotient in the retarded, the number of decibels of hearing loss in the hard-of-hearing, and the extent of loss of sight. Fig. 1 shows a form used in Vancouver.

In older children a report from the school teacher as to academic standing, and general observations on the child's conduct and ability to work, help in the planning for such a child. The result of school counselling is a useful addition. The occupation of the parents is a most helpful inclusion, as it may give a clue to the financial outlook and stability of the family.

TRAVELLING CLINICS

Another great help to the family doctor, especially in remote districts, is the travelling clinic. It brings consultations and specialist services to each area where most needed. It should visit each district at regular set dates, so that these visits can be planned for. The team making up the travelling clinic might consist of a pædiatrician, orthopædic surgeon, eye specialist, and, at intervals, an ear, nose and throat specialist or audiologist and speech therapist. In addition, each district should be visited by a child guidance team, consisting of a child psychiatrist, child psychologist, and social worker. Along with the above teams, nurses are necessary. Tape recorders simplify the making of records. Copies of the specialists' findings go to the family doctor in each area, as well as to the handicapped children's registry, and to any special hospital or clinic where treatment is recommended. The local doctors must be kept informed when the travelling clinic is

Form v.s. 3

PROVINCE OF BRITISH COLUMBIA
PHYSICIAN'S NOTICE OF A LIVE BIRTH OR STILLBIRTH

NAME OF FATHER — Surname — Christian Names

NAME OF MOTHER — Maiden Surname — Christian Names

PERMANENT ADDRESS OF MOTHER — House No. — Street — Name of City or Municipality

PLACE OF BIRTH — Name of Institution — Location

DATE OF BIRTH Hour ..... Day ..... Month ..... Year ..... M.

SEX ☐ Male ☐ Female

Birth.....lbs.....ozs. Weight or.....grams

Single ☐ Triplet ☐ Twin ☐

RACIAL GROUP White ☐ Indian ☐ Other (specify)

Was child born alive ☐ Yes ☐ No

Was resuscitation necessary ☐ Yes ☐ No

Is mother married to father of child ☐ Yes ☐ No

What treatment was given to prevent blindness:

No. of weeks gestation

Total pregnancies (incl.)

Total live births (incl.)

Was mother's blood tested for Rh ☐ Yes ☐ No for syphilis ☐ Yes ☐ No

Month 1 2 3 4 5 6 7 8 9

Name of anæsthetic agent and/or sedation used

Describe operative procedure:

Was labour: Spontaneous ☐ Induced ☐

Describe complications of pregnancy or labour:

Was there a birth injury ☐ Yes ☐ No

Describe birth injury to child:

Congenital malformations ☐ Yes ☐ No

Describe malformations:

Physician's Signature — Physician's Address — Date

Please tear out carbon before mailing

THIS REPORT TO BE SENT WITHIN 48 HOURS TO THE DISTRICT REGISTRAR OF BIRTHS, DEATHS AND MARRIAGES
VITAL STATISTICS ACT SEC. IV.

Fig. 2

arriving. With the local public health nurse or doctor, the patients are examined and reported upon by the various specialists. As a result of such a travelling consultative team, diagnosis may be confirmed, parents convinced about a line of treatment, orthopædic appliances supplied, and glasses and hearing aids ordered.

Emotionally disturbed children seen by the travelling child guidance team are kept under observation and their problems explained to the parents and school authorities. Retarded children may have their intelligence quotient ascertained.

EARLY RECOGNITION OF HANDICAPS

The earlier in life that handicaps are detected the better. If the condition of the infant at birth is mentioned on the card for notification of live birth, many handicaps can been found and promptly treated. If the family doctor has not attended the birth of the infant, he is informed of the condition of the infant and can take steps to institute treatment at once.

The filling in of this form (Fig. 2) has not been found a hardship in British Columbia, and we believe that practically 100% of the births are registered properly.

All handicaps are not recognizable at birth or on first seeing a child. During the early years of the child's life, however, disabilities may be detected by the doctor when the child visits his office, or is seen in its own home for some acute infection. Again, it may be seen at a well baby clinic or examined at school on entry, or during the course of the school years. Each examination therefore brings forth a further crop of disabilities and more children who need help. When children are private patients of the family doctor and are already receiving full and adequate treatment, they are put on the registry's "inactive list", and are used for statistics only. About 20%, however, of all children registered are a problem and will require follow-up through their doctor. More often than not, the help needed is economic or is in regard to their education, the choosing of and training for a vocation and their job placement.

Let us spend a moment or two considering the special problems of the various types of handicapped children.

MENTALLY RETARDED

The largest group are the mentally retarded. The education of these children should start at the earliest age in the home, and the parents should be given the greatest help and encouragement to teach their children the simplest procedures. It is not enough to label a child as mentally defective and fill in a form for an institution, as was customary. Now that such children have been to some extent accepted by the community, the need for residential treatment is reserved for the most severe cases only. Each child's capacity for learning must be carefully assessed by an expert, and home and school instruction given to bring out the maximum in each. The provincial educational authorities must ultimately make themselves responsible for education at all levels of intelligence, and not just for slow learners with an intelligence quotient above 50 as at present.

Until such time as the provincial educational department assumes the full responsibility for all retarded and handicapped children, it may be necessary to start small private schools in each community where six or more retarded children with an intelligence quotient of less than 50 may be taught the simplest essentials of living. This has been done successfully by societies for retarded children in several provinces, and has led ultimately to an allowance being given by the department of education equal to that for normal children, which pays for teachers. At present, however, provincial authorities are reluctant to provide classrooms, but that must come. Instead of being shut away in institutions, a surprisingly high proportion of mental defectives can be taught to be useful citizens and even to earn their own living. Otherwise they would become an intolerable burden on society, and it is our duty to make them self-supporting if possible. The doctor's role is to encourage the parents to have such children seen and assessed by an expert, register them, and put them in touch with the local school for retarded children.

CEREBRAL PALSY

During the years that the cerebral palsied child is having physical treatment, his education may best be given at the treatment clinic. When sufficient physical progess has been made he may enter the ordinary public school and mingle with physically normal children. The diagnosis of cerebral palsy should be made as early as possible, and then each case should be seen and assessed by a team specially trained and interested in this disease. The team should consist of a pædiatrician, neurologist, physical medicine expert, psychologist, specially trained physiotherapist, school teacher, social worker, speech therapist, ophthalmologist and audiologist. It may take several visits – in fact sometimes several weeks – to make certain of the child's mental and physical potentialities, whether sight and hearing are normal, and how much and what kind of treatment and education are best suited to such a case. It is only by the use of trained staff and the careful recording of results that progress can be assessed. Every child with cerebral palsy should be given a chance of a thorough assessment of his case by such a team at least once in his life. The occasional attendance at a good clinic once or twice a year for those cases from a distance is much better than nothing.

THE DEAF CHILD

Great advances have been made in the treatment of the deaf. The emphasis on sign language has been lessened, and also on lip reading. There is great concentration now on teaching the child to hear with the help of a hearing aid. This is best done at as early an age as possible, even before one year. This has been found highly successful, and the child's speech has been much improved with this method. Children with unsuspected hearing loss may be found by the travelling audiologist, who is an essential part of the service to every community.

The necessity for residential schools for the deaf has been lessened by the early detection and training of these children, and it is hoped that many will be able to attend the ordinary public school in future.

SQUINT AND DEFECTIVE VISION

As many as 25% of high school children may have some degree of defective sight. Certainly, the careful testing of eyesight is most necessary, since inattention and poor conduct at school are often due to this. Early attention to squints to correct them will usually prevent loss of sight in the squinting eye, as well as the psychological trauma of such a defect. Sight-saving classes, where special books with large print are made available, are in use everywhere. Orthoptic eye exercises, both before and after squint operations, appear to be of the greatest help. A resident or day school for the deaf and blind child is a necessity for certain cases.

SPEECH DEFECTS

Speech defect cases require a thorough examination. Some may be due to emotional difficulties. Considerable treatment is necessary in other cases. The situation needs to be carefully explained to the parents and teachers, and their co-operation obtained. Such conditions should not be allowed to run on without an expert having made a thorough search for the underlying cause.

ORGANIZATION OF GROUPS TO HELP SPECIAL HANDICAPS

In order to bring about progress in the treatment of certain special disabilities, it may be necessary and desirable to form groups or societies to speak for these handicapped children. The medical profession must show leadership in these groups. Each group of parents may feel that their child's disability is being neglected unless they are allowed to take some personal part in an organization. In comprehensive societies for crippled children it is sometimes best to have sections for each type of handicap, where parents get the chance to express themselves freely and press for increased facilities to be made available for their child.

EDUCATION

It is the doctor's duty to point out to the parents of all his handicapped patients the value and necessity of as much education as possible. A handicapped person needs to be better educated than a normal one, if he is to compete in employment. A realistic outlook as to the sort of vocation possible should be stressed, so that parents and the growing child will aim at something which it is within his ability to achieve.

VOLUNTARY FUND-RAISING AGENCIES

How may the doctor use voluntary fund-raising agencies to help his patient? There are a variety of ways in which this child may need help. Transportation to or from school or clinics or to nearby cities for specialist treatment requires organizing, and may require financial assistance. It may be necessary to establish a hostel for mother and child to stay in when visiting a city for diagnosis and short-stay treatment, or use foster homes, especially for those in the low income group. Splints, special boots and wheel chairs, glasses, hearing aids and many other appliances may be needed. There is often a local group in your own town or village able to supply the money for what is necessary. If not, the handicapped children's registry should know where to advise you to make application.

CONCLUSIONS

In conclusion, in order to have a co-ordinated program for handicapped children, it is necessary for the family doctor to play a much larger part than he has heretofore been willing or able to do. These are the steps necessary to get this co-operation.

1. A complete registry of handicapped children should be backed by the medical profession. In this way, the nature of the children's handicaps and their numbers will be discovered and steps taken to supply services. It may be found that the estimates of the numbers of the handicapped are very far from the truth. Having the factual data, the registry is in a strong position to bring deficiencies in services before the government and public. As a result, deficiencies will be rectified and each child can be sent to the hospital or clinic where he will obtain the best treatment for his particular disability.

2. The introduction of questions as to the condition of the infant at birth on the card for notification of birth, will bring about early detection of congenital malformations and injuries and focus attention on the newborn infant. Family doctors and obstetricians can help by answering these questions fully.

3. Travelling clinics manned by teams of specialists in the disabilities of the newborn and school-aged children will make diagnosis more perfect and start treatment at an early age. Here again the family doctor can help by using or requesting the establishment of these clinics where he can get help for his patient.

4. When the medical side of each case has been as thoroughly dealt with as possible, the family doctor must be brought more into the picture when the child's education, vocational training, and suitable employment are being discussed. The team approach to these problems is the one recommended, as in other medical problems.

5. From start to finish, the family doctor must be the champion and best friend of the handicapped child, and seek out and use every facility available for his patient. He should never cease a flow of encouragement to the parents and child; having done this, what more reward can he have than the grateful thanks of a handicapped child?

SHORT COMMUNICATIONS

MENTAL DEPRESSIVE EPISODES DURING RAUWOLFIA THERAPY FOR ARTERIAL HYPERTENSION, WITH SPECIAL REFERENCE TO DOSAGE*

E. BOLTE,† J. MARC-AURELE,‡
J. BROUILLET,† P. BEAUREGARD,†
M. VERDY† and J. GENEST, *Montreal*

IN A PREVIOUS REPORT published in this *Journal* in 1956,[1] we showed that mental depressive states occurred in 30 out of 195 hypertensive patients during administration of various Rauwolfia extracts.

*Clinical Research Department, Hôtel-Dieu Hospital, Montreal. Work supported through grants of the Ministries of Health (Federal-Provincial Plan) and the Ciba Company, Montréal. Rauwolfia preparations used in the study were generously supplied through the courtesy of Dr. Walter Murphy, Ciba Co., Montreal (Serpasil); Mr. H. G. McWaters and Mr. G. Garstone, Ricker Laboratories (Serpiloid, Rauwiloid); and Mr. H. Comte, Squibb Co., Montreal (Raudixin).
†National Research Council Fellow, 1957-58.
‡Public Health Medical Research Fellow, 1957-58.

No depressive state occurred in a group of 100 hypertensive patients receiving hypotensive therapy consisting of ganglionic blocking agents and hydralazine. The average dose of reserpine administered was 1.5 mg. daily, with a range of 0.75 to 4 mg. Eighty per cent of all cases of mental depression were secondary to reserpine administration, whereas only 20% occurred in patients receiving either the alseroxylon fraction (Rauwiloid) or the whole root crude extract (Raudixin).

We wish in this report to compare the incidence of mental depressive episodes in hypertensive patients receiving reserpine at a level of 0.5 mg. and less per day with that found in patients receiving 0.75 mg. and more per day, and also in those receiving the whole extract or the alseroxylon fraction.

A mental depressive episode is defined as a combination of several of the following complaints: feeling of sadness and discouragement, lack of ambition and energy, crying spells without motivation, loss of interest in usual activities, worry over trifles, "making mountains out of molehills", indecision, anxiety, sensation of chronic fatigue, inability to concentrate, and withdrawal from the environment. This study includes all hypertensive patients followed up in our clinic and having received one or more rauwolfia extracts, alone or in combination with other hypotensive drugs. Of a total of 270 hypertensive patients, 200 were women with a mean age of 51; 70 were men with a mean age of 49. The minimum duration of administration was one month (with the exception of one person who developed a mental depression after two weeks), with a maximum of three years. Since administration of rauwolfia was combined in most patients with other hypotensive agents, no attempt was made to evaluate the hypotensive effect of reserpine given at a dosage of 0.5 mg. or less per day in comparison with a dosage of 0.75 mg. or more per day. Of these 270 patients, 228 received only one extract and 42 patients received more than one extract, but never simultaneously. There were 364 courses of various rauwolfia preparations given continuously for more than one month.

Seventy-seven depressive episodes occurred in 63 patients; 13 patients had two depressive episodes and one had three. Of these 63 patients who exhibited mental depressive episodes, 47 were women and 16 were men.

Forty-two of these 63 patients were between the ages of 40 and 60, the period of life during which mental depression is most common. The mean age was 51, with a range of 20 to 73. As indicated in Table I, the incidence of mental depression with reserpine at a dosage of 0.75 mg. or more per day was 31%, approximately four times the incidence with dosages of 0.50 mg. and less per day. With the alseroxylon fraction, mental depression occurred in 13% of patients receiving 6 mg. or less per day and in 20% of patients receiving 8 mg. or more per day. In patients receiving the crude root extract, the incidence of mental depression was 16% in a dosage range of 100 to 400 mg. per day.

TABLE I.—INCIDENCE OF MENTAL DEPRESSION IN 270 HYPERTENSIVE PATIENTS RECEIVING RAUWOLFIA EXTRACTS (1954 - 1957)

	*No. of courses**	*No. of depressive episodes*	*Per cent*
Reserpine			
0.75 mg. and more/day	163	51	31
0.5 mg. and less/day	80	6	7.5
Alseroxylon fraction			
8 mg. and more/day	32	6	20
6 mg. and less/day	15	2	13
Crude root extract			
300 mg. and more/day	37	6	16
200 mg. and less/day	37	6	16
	364	77	

*More than one month of continuous administration.

These findings establish clearly that mental depression is commoner in the group of patients receiving reserpine at dosages of 0.75 mg. or more per day. High dosage of reserpine can be incriminated without any doubt in the causation of mental depression. One point which cannot be clarified in this study is whether reserpine at dosages of 0.5 mg. and less per day is as effective in lowering high blood pressure as it is at higher dosages. The period of time between onset of administration of rauwolfia extract and occurrence of the depressive state was on the average 6.7 months, with a range of 0.5 to 38.5 months.

Most patients recovered completely after cessation of rauwolfia extracts, occasionally with the addition of a centrally stimulating drug consisting either of amphetamine or methyl-phenidylacetate (Ritalin*). In 15 patients receiving reserpine, mental depression disappeared after dosage was lowered to less than 0.5 mg. per day.

Four patients completely recovered from their depression despite continuation of rauwolfia at the same dosage. Nine patients needed admission to hospital and electroshock treatment; eight of these were receiving reserpine.

The present survey confirms the reports of other workers,[2-6] and indicates that mental depression encountered in patients receiving extracts of rauwolfia is due mainly to two factors: the dose given and a previous history of mental depression or a psychologically disturbed personality. Sex and age do not appear to play any role in the occurrence of mental depression. The higher incidence of depressive episodes in women in the present report is parallel to the predominance of female patients in our clinic.

SUMMARY

A study of mental depression was made in 270 hypertensive patients receiving various extracts of *rauwolfia serpentina* in our clinic. Seventy-seven depres-

*Kindly provided by Dr. W. Murphy, Ciba Co., Montreal.

sive episodes were encountered in 63 hypertensive patients. Fifty-one mental depressive episodes occurred in patients receiving reserpine at dosages of 0.75 mg. or more per day. Because of the beneficial effect of rauwolfia in patients with arterial hypertension, the present study makes it advisable to give reserpine at a dosage of 0.5 mg. or less per day and withhold rauwolfia extracts from patients with a previous history of depressive states or depressive moods.

We are pleased to express our sincere thanks to Misses Fernande Salvail and Renée Dansereau, R.N., for their invaluable collaboration.

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THE TREATMENT OF ACUTE GONORRHŒAL URETHRITIS WITH A LONG-ACTING PENICILLIN TABLET (FALAPEN)

AUGUSTE HEBERT, M.D.,* *Montreal*

IN RECENT REPORTS[1, 2] it has been shown that the administration of one 500,000-unit long-acting penicillin tablet (Falapen) provided continuous serum penicillin levels for 12 hours in a large majority of patients. It has also been shown that one tablet every 12 hours for five or six days was effective in clearing up infections caused by penicillin sensitive organisms.[1]

The present report deals with the use of this preparation in the treatment of acute gonorrhœal urethritis.

Eleven male patients were seen in the outpatient department where the interval between time of exposure and time of onset of urethritis was recorded, and a smear of the urethral discharge was examined. Each patient was then given eight tablets and instructed to take one tablet every 12 hours and to report back for examination in five to seven days. On reporting, the patient was questioned concerning the length of time required for the discharge to stop, and examined for signs of disease. Except in Case D 3028, where a few shreds were noted in the urine and a drop of clear secretion was obtained, which, however, on smear was negative for gonococci, no evidence of infection was found. The data are shown in Table I.

It is noteworthy that the gonococcus remains sensitive to penicillin and that gonorrhœa may be effectively treated by the administration of penicillin by the oral route.

SUMMARY

Eleven patients with acute gonorrhœal urethritis were treated with a 500,000-unit long-acting penicillin tablet (Falapen), in a dose of 1 tablet every 12 hours for 4 days. One patient was clear of discharge in 12 hours, six patients in 24 hours, two in 48 hours, and one in 72 hours. One patient had a few shreds in the urine and a drop of secretion which on smear showed no gonococci.

TABLE I.

Date, 1958	*Patient No.*	*Exposure*	*Time of onset of urethritis before consultation*	*Smear gonococci*	*Urine*	*Falapen*	*Discharge stopped (hours after starting treatment)*
Oct. 15	D2357	3 days previously	12 hours	+	Cloudy	1 tablet every 12 hrs. for 8 doses	24 hours
Oct. 15	C 14280	8 " "	24 hours	+	"	"	24 "
Oct. 17	D 2467	8 " "	2 days	+	"	"	24 "
Oct. 20	117837	4 " "	3 days	+	"	"	48 "
Oct. 20	D 2633	6 " "	24 hours	+	"	"	48 "
Oct. 27	C 81469	4 " "	2 days	+	"	"	24 "
Oct. 27	C 96892	3 " "	12 hours	+	Cloudy, shreds	"	12 "
Oct. 27	C 3443	5 " "	2 days	+	Cloudy	"	24 "
Oct. 27	D 3028*	6 " "	2 days	+	"	"	Clear drop present Nov. 5
Oct. 29	D 3153	2 weeks "	6 days	+	"	"	72 hours
Oct. 29	D 3152	3 days "	24 hours	+	"	"	24 "

*This patient was re-examined on November 5, 1958, when a few shreds were noted in the urine and a clear drop of discharge was obtained. A smear from this was negative for gonococci. He was given a sulfonamide and the discharge cleared up in a few days' time.

ADDENDUM

Since submission of this communication for publication, we were able to obtain smears following prostatic massage from 5 patients 14 days after completing treatment. All were negative for gonococci.

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*From the Department of Urology, L'Hôpital St-Luc, Montreal.

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NO GOING BACK

Everyone knows that the man who has profited least from the introduction of the National Health Service in the United Kingdom is the general practitioner. The threat of withdrawal from the N.H.S. made by the General Medical Services Committee of the British Medical Association in February 1957 was related solely to general practitioners, and this committee later began a study of alternative schemes for the provision of medical care in the event of such a withdrawal.

With the idea of getting an outside opinion on the situation, this B.M.A. Committee last May invited Sir Frank Newsam, a retired civil servant of proven organizational and administrative ability, "to investigate any deficiencies in, and frustrations arising from, the present scheme for providing family doctors' services in the National Health Service, and to suggest practical modifications or alternative services".

Sir Frank has produced his report, and a very unpalatable one it is. Indeed it is clear from the tone of the editorial and the statement by the B.M.A. Council accompanying Sir Frank's report in the January 17 issue of the *British Medical Journal* that only the British virtue of fair play has led to its appearance in print. For not only does the author fail entirely to present a scheme for the alleviation of the family doctor's grievances (a well-nigh impossible feat in the few months allotted to him), but he also admonishes the profession like an Old Testament prophet – and of course provokes much the same reaction in his hearers.

"The National Health Service," says Sir Frank, "is here to stay. The welfare state is a continuation of the spirit which won the war. It is unrealistic of doctors to think of withdrawing from the National Health Service. The inevitable result would be the formation of a fully salaried service."

He regards any framing of an alternative scheme for providing family doctors' services as a function of Government on advice tendered by the profession as a whole. But he also records his impression that the public is no longer interested in the ten-year quarrel between the doctors and the Government, and would not easily forgive a concerted effort to wreck the N.H.S. or any vital part of it.

"In a democracy such as ours," he says, "any struggle with Government can be won only by a successful appeal to the people. In the case of the family doctors that means an appeal to their patients—a counsel of despair for a profession with authoritarian traditions."

But in spite of these stern pronouncements, the reporter obviously realizes the great disabilities under which the British general practitioner works, and states that no reform in the N.H.S. is more urgent than an improvement in the family doctor service, though he is quick to point out that "the better the doctor (clinically), the fewer his frustrations and grievances."

The report deserves careful study by Canadian physicians, particularly those serving on such bodies as committees on economics, but it must of course be taken for what it is—an expression of opinion by a retired civil servant, who is bound to feel that in general what Government does is right, and better done than the work of a private body.

The thing that stands out from this report is the obvious assumption that in national health services there is no going back. The only alternative method of remuneration envisaged by Sir Frank is by a tightening of the civil service screw and the creation of a complete salaried service. He may be wrong in this, but his viewpoint does suggest that in setting up a health service the profession must decide what it wants from the start and act on the sound medical principle of adopting preventive rather than curative measures.

Editorial Comments

A PSYCHIATRIST SPEAKS HIS MIND

In his presidential address to the Australasian Association of Psychiatrists about a year ago, Cedric Swanton not only spoke his mind but also got a few things off his chest (*M. J. Australia*, 2: 373, 1958). The issues raised by him are of interest to the profession at large, for he points out quite rightly that "any doctor who does not know something of psychiatry does not know his job." He warned us not to apply psychotherapy indiscriminately, and to learn to recognize those patients who need their physical illness and should be allowed to have it. The patients have an ego and may find it intolerable to be told that they are "neurotic". Such people, for whom psychological treatment is impossible, are often found among intellectuals.

With the increase in pensions and other social benefits, we are more frequently required to recognize those who are trying to abuse these welfare

aids without being unjust to those who are using them as a temporary crutch. If humoured for a while, many of the latter group will make a good recovery and adjust once again to life. The best we can do in an individual case is to act honestly from our own conviction, arbitrate as best we can in the medical compensation case, and hope that there will be more justice than injustice.

Swanton obviously does not share the enthusiasm for many of the "wonder drugs" and warns us to resist public pressure when it comes to treating one's own patient. Nor are doctors immune to the craving for the great panacea which is behind this drive. By reasserting his authority the doctor will increase the public's respect for the profession. On the subject of ataractics and tranquillizers, Swanton gives a masterly and thought-provoking description of the present state of affairs in the treatment of mental diseases. The problems that have arisen since the introduction of these drugs are manifold; not the least of them concerns the patient who has become tractable under drug treatment and is now being sent home on a maintenance dose of the drug. This patient was originally certified, he may have been in hospital for a long time, and the family is now required to make a new adjustment to the presence in their midst of a person who has to be supervised and for whom there is no certainty that he will remain well. The family's feeling of guilt for having certified the patient in the first place complicates matters, and there will be reluctance in many cases to send the patient back to hospital even though he is obviously relapsing.

And what of the treatment of the anxiety states, tension and similar conditions? Swanton states flatly, and we believe correctly, that these conditions have always been with us and always will be. It is the price we pay for being human beings, and this capacity to modify instinctual behaviour and to tolerate resultant frustrations and anxiety places us above the level of the lower animals. The demand to be free of anxiety is common to us all, but tranquillity and happiness lie within oneself and are not to be found in a bottle. He quotes the report of the Committee on Public Health of the New York Academy of Medicine which asks "But when has life ever been free of stress? In the long run is it desirable that a population be ever free from tension? Should there be a pill for every mood and occasion?" These drugs appeal to the dependence in all of us, says Swanton, and we have to resist this regression to the utmost if we don't want to deteriorate into a race of dependent addicts. Is is fair to exonerate the medical schools of any blame for over-prescribing, as Swanton does? Is it not the duty of medical school to teach us how to reason, how to discriminate in our prescribing, and to go about incorporating new drugs into our armamentarium? Should they not teach us how to counter intelligently any pressures from manufacturers, press and public? Must we find out for ourselves how to cope with the patient who brings us an article from the "Readers' Digest", with the request that we read it, so as to find out the latest treatment for his or her ailment?

Swanton refers to the Wherry Memorial Lecture delivered by Arthur Proetz the previous year, in which the dangers of indiscriminate use of new and unfamiliar drugs, and the effects of multiple diagnostic and therapeutic procedures, on the internal environment of the patient are graphically described. In a period in which one thousand patients were admitted to a large hospital more than 50 major toxic reactions and accidents were encountered! Proetz's final sentence concludes Swanton's addess: "I have read somewhere that the latest wonder drug is so powerful you cannot take it unless you are in perfect health!" This may sound facetious to some but is a warning well worth pondering over from time to time.

W. GROBIN

"ROUTINE" BLEEDING AND CLOTTING TIMES

Diamond and Porter of the Department of Pediatrics, Harvard Medical School, report the results of a study, the purpose of which was to show that "routine determinations of bleeding and clotting times done before operations, ostensibly to screen out patients who are bleeders, fail to do this," and make a plea that they be abandoned (*New England J. Med.*, 259: 1025, 1958).

Three groups of children were examined and a variety of tests were performed on their blood. These included bleeding time by the Ivy method, clotting time by the Lee and White method, Quick prothrombin time, prothrombin consumption and thromboplastin generation. In many cases they performed direct capillary microscopy. One group of nine children had been found to have abnormal bleeding and clotting times before operation, but neither the special tests nor the familial and past history revealed a bleeding tendency. Group two, who had normal bleeding and clotting times but bled after tonsillectomy or dental extraction, also had a normal personal and family history and their special tests were negative. The third group also had normal clotting and bleeding times, even by tests with careful attention to detail, and yet these 19 children had a known hæmorrhagic disease (12 classical hæmophilia and 7 Christmas disease). Five had bled after a surgical procedure. Their special tests were of course positive and so was the family history.

This is a striking demonstration of the uselessness of bleeding and clotting times as screening procedures preoperatively, and confirms the value of a carefully obtained personal and family history. The authors state very emphatically that they have "yet to see a patient with a congenital coagulation defect who did not have a significant history suggestive of this, by the time he reached the age of two years, no matter how mild the disease". If such evidence is obtained they recommend that a whole battery of tests be done to confirm or rule out the presence of congenital bleeding tendency. Examination of the blood smear for platelets will help to rule out an acquired coagulation defect. The authors mention that another article has recently appeared which draws attention to

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the futility of measurement of bleeding and clotting time as routine examinations.

It is obvious that with newer knowledge and refinement in tests, many of the older tests are bound to fall by the wayside or to lose the significance they were once thought to possess. It is reassuring, in all this progress, to find that the only procedures that have stood the test of time and have constantly gained in stature are a carefully taken personal and family history and a thorough physical examination. These of course depend for their results on the experience of the physician, but this experience can only grow if he practises this art of history taking and physical examination, which is the art of diagnosis.

THYROID TUMOURS FOLLOWING IRRADIATION

Two recent articles in the *British Medical Journal* suggest that ionizing radiation applied to the area of the thyroid gland may lead to the development of growths of that tissue at a later date.[1, 2] An editorial in this same journal outlines the history of this concept.[3] An article by Duffy and Fitzgerald in the *Journal of Clinical Endocrinology* in 1950 was one of the first to suggest this idea. In a series of 28 cases of thyroid cancer, they found that nine had been preceded by radiation to the neck between four and 18 months of age.[4]

At one time it was common practice to irradiate the neck area for such things as nævi, hyperthyroidism and thymic enlargement. At the present time this therapy is still used in acute thyroiditis and to treat keloid formation in neck scars.

From the available reports, ionizing radiation in this region seems most dangerous during infancy; at this time a small dose (as little as 130 r) may be followed by tumour formation.[1-3] Most of the carcinomas following x-ray therapy in childhood have been predominantly papillary in type,[1] and this type of carcinoma of course has the best prognosis.[5, 8]

Few cases have been reported of cancer of the thyroid developing after radiation therapy to the adult gland. Professor G. M. Wilson, of Sheffield, now reports one case developing in a girl who was irradiated at age 26 for thyrotoxicosis. Thirty-seven years later, she developed an undifferentiated anaplastic carcinoma of the thyroid.[1] Goolden, from Hammersmith Hospital, London, reports two cases. In one case, a woman was irradiated at age 18, and found to have a follicular carcinoma of the thyroid at age 36. In another case, a woman received x-ray treatment at age 28 for exophthalmic goitre. Forty-one years later, she developed a follicular carcinoma of the thyroid gland.[2]

Radioactive iodine has been used rather widely since 1942,[3] and thyroid carcinoma has been produced in rats by the administration of radioactive iodine. A goitrogen given at the time produces the tumours more readily.[1] It is felt that clinical dosage schedules of radioactive iodine may be of sufficient intensity to produce premalignant changes. Because of the long latent period of thyroid cancer (approximately 20 years), this entity may be more common in the near future.[3]

As susceptibility to this lesion seems more common in the younger age groups, one should hesitate to apply ionizing radiation to the neck area in infants and children, and this prohibition would include the use of radioactive iodine for diagnostic purposes. Common sense should prevail, however, since the risk of developing cancer in any one individual is probably small.

It is also possible that radiation acting as a carcinogen may be supplemented by various factors which are co-carcinogens. Goitrogens conceivably may act in this way. Crile has also raised the question of hormone dependency in thyroid cancer. Goitrogens, by producing hypothyroidism, may cause increased production of thyroid stimulating hormone (TSH) and aggravate an existing thyroid cancer.[7] At any rate, the risks of using such drugs in children should be weighed against their advantages.

Another point is raised by Professor Wilson. In two of his cases, after the use of radiation an adenomatous condition, presenting some features of neoplasia, was found.[1] This raises the question of adenomas preceding malignant change. At any rate, we may wonder whether the same stimulus can produce an adenoma or a carcinoma under slightly different conditions.

Professor Ian Aird, whose wide clinical experience should be respected, feels that some reported cases of thyroid carcinoma, following irradiation in infancy, may originally have been undiagnosed carcinomas.[4] The natural history of papillary carcinoma would support this condition.[5, 8]

Another consideration is that of surgical removal of the tumour. How extensive should the operation be? If malignant change is to follow radiation, surely this is not confined to one part of the gland. Professor Aird feels that thyroid cancer warrants total thyroidectomy.[9] The type of cancer, the degree of involvement of surrounding structures, and the clinical condition of the patient, must often dictate the extent of surgical removal.

Thus practising physicians should now be aware of the possible dangers of irradiation of the neck area in childhood. All cases of thyroid tumour formation preceded by irradiation should be reported in the literature, and the history, in the case of a thyroid swelling, should include asking both the patient and the parents about previous radiation therapy to the neck.

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Medical News in brief

PINEAPPLES AND DYSMENORRHŒA

The stem of the pineapple contains a proteolytic substance which can be extracted in crystalline form and is then called bromelain. It has a mucolytic effect on the cervix, and Simmons (*Lancet*, 2: 827, 1958) reports a favourable effect on spasmodic dysmenorrhœa. He poured a freeze-dried preparation, dissolved in water and warmed, into the vagina and allowed it to bathe the cervix for five to eight minutes. Some patients treated themselves at home with a simple rubber bulb and glass tube. The effect on the cervix was to soften it and make it more vascular. The softening seemed to extend as far as the internal os. After treatment, vagina and cervix were found to be clear of discharge or mucus.

Simmons has now used the substance without complications on 89 occasions in 65 patients over a period of ten months. In 23 cases treatment was given before an operation or before cervico-hysterography. In 30 cases spasmodic dysmenorrhœa was treated with good results in 42 out of the 48 occasions on which it was used. Some relief was also obtained by patients with congestive dysmenorrhœa. The optimum time of application was just at onset of, or shortly before, the period, and in some cases relief persisted for as many as four cycles afterwards. Treatment did not inhibit ovulation, and there was no evidence that the preparation would act as an abortifacient.

The dramatic effect of bromelain on the colicky pain at the onset of a period is partly due to relaxation of the smooth muscle of the cervix.

CLUSTER HEADACHES

The syndrome now known as "cluster headaches" has had a variety of names. It was called "red migraine" in the last century, "erythromelalgia of the head", "Sluder's headache", and, more recently, "Horton's headache". There is general agreement that it is due to vasodilatation in the branches of the external carotid artery, although this would not explain satisfactorily all the manifestations of this syndrome. A series of 50 cases is compared by Friedman and Mikropoulos (*Neurology*, 8: 653, 1958) with several other representative series by such authorities as Horton, Symonds, and Klunke. In all series there was a marked predominance of males over females (4.5:1), the bouts lasted 1-10 weeks, there were 1-8 paroxysms of pain lasting ½ hour-2 hours each in the 24 hours, and there were intervals without headaches of 2-24 months' duration. The commonest location of the pain was orbital, more frequently on the right, and it was usually associated with nasal congestion, lacrimation and ocular injection.

The present authors believe that this entity is related to migraine, and found that ergotamine was effective symptomatically. They mention that two of their patients who were under psychotherapy have been free of headaches for 2 and 2½ years respectively. In all others, no prophylactic treatment has been of value. The condition should be differentiated from typical and atypical neuralgias of the head as well as from classic migraine.

THE NATURAL HISTORY OF HYDROCEPHALUS

Of 182 patients with hydrocephalus seen by one neurosurgeon (Wylie McKissock) between 1938 and 1957 at the Atkinson Morley Hospital, Wimbledon, England, and the Hospital for Sick Children, Great Ormond Street, all but three were traced by Laurence (*Lancet*, 2: 1152, 1958). None of these patients had received any surgical treatment. In most cases the hydrocephalus had been acquired through perinatal trauma, anoxia or infection. It often developed insidiously without an obvious cause, but it is assumed that in these cases also a missed mild meningitis or perinatal injury was responsible. In four cases a tumour was unexpectedly found at necropsy. The disease usually began in the first six months of life and lasted from three months to two years. In a few children the hydrocephalus began at a later age, generally following meningitis, and in a number of children the disease remained slowly progressive for years. Of the 89 patients who died, the majority did so before the age of 18 months. The cause of death was hydrocephalus in 42 cases, intracranial infection in 13 cases and a related complication in 29 cases.

In nine cases the condition is still progressive but 81 of the children are alive and well, with the hydrocephalus arrested. Intelligence was assessed in these 81 children, and the degree of physical handicap was estimated; 33 were of normal intelligence and 27 had very little or no physical disability. The authors believe that if a hydrocephalic child survives and has a spontaneous arrest of his condition he has a 75% chance of being educable, and a 57% chance of being taught in a school for normal children. In view of the 46% spontaneous-arrest rate, it may be necessary to reassess the value of surgery in this condition. This study indicates a more hopeful prognosis for an appreciable number of children with hydrocephalus.

SPORADIC CRETINISM WITH OTHER CONGENITAL MALFORMATIONS

In 1908, McCarrison described cases of endemic cretinism combined with signs of cerebral diplegia. This condition which he called "nervous cretinism" has since been repeatedly described in small numbers of patients. Hellinga of Amsterdam (*Nederl. tijdschr. geneesk.*, 102: 2423, 1958) describes five cases of congenital absence of thyroid function in which certain symptoms occurred which cannot well be explained on the grounds of thyroid deficiency. These included failure of mandibular development with retrognathia, nasal speech, progressive shortening of the calf muscles resulting in walking on the toes, and various anomalies in the feet.

Hellinga speculates on the cause of this condition, pointing out three possibilities: (1) failure of supply of fetal thyroid hormone during intrauterine life; (2) hypothyroidism in the mother, though this was not found in any relatives of the present series; (3) a genetic and familial factor. He draws attention to the similarity between this syndrome and that of Turner, in which failure of function of the testes or ovaries is associated with skeletal and soft part anomalies.

(Continued on advertising page 54)

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NEW DRUGS

As an aid to prescribers, we are starting a new section on drug preparations, which will consist of two parts. The first part will be a listing of certain products, based on information received from Dean F. M. Hughes, Faculty of Pharmacy, University of Toronto, and the *Canadian Pharmaceutical Journal*, to whom we owe thanks. The first of such listings appears below.

The other feature will be a number of monographs on new products of particular interest, selected and described by competent experts. The first of these monographs will appear in the issue of March 1.

DULSANA COMPOUND, (N), Frosst

Description.—Each 5 c.c. teaspoonful contains: Paracarbinoxamine maleate 2 mg., ephedrine hydrochloride 4 mg., codeine phosphate 10 mg., ammonium chloride 100 mg., chloroform 25 mg., menthol 0.25 mg., flavoured syrup base q. s.

Indications.—For the symptomatic relief of cough in pharyngitis, laryngitis, tracheitis, bronchitis, pneumonia, bronchiectasis, bronchial asthma, whooping cough, smoker's cough and the "cough habit of nervous origin".

Administration.—Adults: One or two teaspoonsful (5-10 c.c.) three or four times daily, as required. Children: 6-12 years: one-half to one teaspoonful (2.5-5 c.c.) three or four times daily, as required; children under six years: as recommended by the physician.

How supplied.—Bottles of 3, 16 and 80 fl. oz.

AMINET Suppositories, (Pr), Ames

Description.—Full strength; half strength (for persons over 80 lb.); ¼ strength (children over 40 lbs.).

Aminophylline	*Pentobarbitone Sodium*	*Benzocaine*
0.5 g.	0.1 g.	0.06 g.
0.25 g.	0.05 g.	0.03 g.
0.125 g.	0.025 g.	0.015 g.

Indications.—Bronchial asthma, cardiac asthma, adjunct in congestive heart failure.

Administration.—One suppository of appropriate strength one to three times daily.

How supplied.—Each strength, 12's.

TRAL with Phenobarbital Gradumets, (Pr), Abbott

Description.—Each Gradumet (long-acting dosage form) contains: Tral (hexocyclium methylsulfate) 50 mg., phenobarbital sodium 30 mg.

Indications.—For combined anticholinergic-sedative action in peptic ulcer and gastro-intestinal disorders associated with hyperacidity and hypermotility and in certain spastic conditions of the intestinal and biliary tracts.

Administration.—Initially, one twice daily preferably before lunch and at bedtime. Carefully adjust dosage to the individual patient.

How supplied.—50, 500.

DECADRON, (Pr), M. S. D.

Description.—Dexamethasone (16-alpha-methyl-9-alpha-fluoro-prednisolone), synthetic adrenocortical steroid 4 to 6 times more potent than 6-methyl prednisolone, 6 to 8 times more potent than prednisolone, 25 to 30 times more potent than hydrocortisone; but without proportionate increase in undesirable side effects.

Indications.—Conditions that respond to adrenocortical steroid therapy.

How supplied.—0.5 mg. tablets, scored, yellow, 30 and 100. 0.75 mg. tablets, scored, green, 30 and 100.

NITROSTABILIN, B. D. H.

Description.—Glyceryl trinitrate in stabilized form, tablets of 1/100 gr.

Indications.—For prevention and relief of angina pectoris.

How supplied.—100, 1000.

PROMATUSSIN Expectorant, Wyeth

Description.—Each teaspoonful (5 c.c.) contains: promethazine hydrochloride 5 mg., dextromethorphan hydrobromide 10 mg., fluid extract of ipecac 0.17 min., potassium guaiacol sulfonate 44 mg., citric acid, sodium citrate, chloroform and glycerin in a pleasantly flavoured syrup base.

Indications.—Provides sedative and antitussive effect for the control of cough associated with colds, allergy or minor upper respiratory infections.

Administration.—Suggested dose: Adults: one or two teaspoonsful every 4 to 6 hours. Children: one-half to one teaspoonful every 4 to 6 hours.

How supplied.—16 and 80 fl. oz.

BARRIERE-MYCIN, B. D. H.

Description.—A topical preparation containing 0.5% neomycin sulphate in a non-irritating silicone cream base.

Indications.—Prophylaxis and treatment of cutaneous pyogenic infections.

Contraindications.—Should not be applied in or near the eyes.

Administration.—Apply to the affected parts two or three times daily, rubbing in gently, if possible, until absorbed.

How supplied.—Tubes of ½ oz. (approx. 15 g.) and 1 oz. (approx. 30 g.).

SOFRAMYCIN NEBULISER, Ang.-Fr.

Description.—Each c.c. contains: Soframycin 12.5 mg. (1.25%); Gramicidine 50 mcg. (0.005%); Phenylephrine HCl 2.5 mg. (0.25%).

Indications.—Acute coryza, rhinitis, rhino-pharyngitis, sinusitis.

Administration.—4 or 5 sprays into each nostril every 2 or 3 hours.

How supplied.—Squeeze bottle atomizer, 15 c.c.

DERONIL, (Pr), Schering

Description.—Each scored, oval tablet contains: 0.75 mg. Dexamethasone (16-alpha-methyl-9-alpha-fluoro-prednisolone).

Indications.—As for prednisolone: the various rheumatic, allergic, dermatological, ocular and other diseases known to be responsive to the anti-inflammatory corticosteroids. Similar to prednisolone but more potent anti-inflammatory therapeutic action. Enhanced anti-inflammatory effect with lower dosages and with decrease of unwanted effects such as sodium retention and œdema.

How supplied.—30, 100.

PREDNYL Tablets, (Pr), U.S. Vit.

Description.—Each tablet provides: 1 mg. prednisolone, 5 grains salicylamide, 33.3 mg. water-soluble citrus bioflavonoid compound, 33.3 mg. ascorbic acid, 50 mg. aluminum hydroxide.

Indications.—For relief of pain, muscle spasm, inflammation and swelling in rheumatoid arthritis, fibrositis, osteoarthritis, bursitis and other inflammatory and rheumatoid conditions. Protects against steroid-induced capillary damage (gastric hæmorrhage, ecchymoses, etc.), gastric disturbance, vitamin C depletion.

Administration.—As a general rule, the initial dose is 1 to 3 tablets, 4 times daily, preferably after meals and at bedtime. Dosage should be reduced *gradually* to minimum effective maintenance levels, usually 3 to 6 tablets daily in divided doses.

How supplied.—100 and 500.

COSA-TETRACYN PEDIATRIC DROPS, (Pr), Pfizer

Description.—Contains tetracycline, with glucosamine.

Indications.—Wide variety of common infections of the respiratory, gastro-intestinal and urinary tracts, as well as other organs and tissues.

Administration.—Children: average infections 5-6 mg./lb./day; severe infections 10-12 mg./lb./day. Adults: average infections 250 mg. 4 times daily; severe infections 250 mg. 6-8 times daily or 500 mg. 3-4 times daily.

How supplied.—10 c.c., 100 mg. per c.c. (5 mg. per drop) calibrated dropper, dry powder.

(To be continued)

Men and Books

NOTHING NEW UNDER THE SUN*

The thing that hath been is that which shall be; and that which is done is that which shall be done, and there is no new thing under the sun. (Ecclesiastes, 1:IX).

WALTER DE M. SCRIVER, M.D.,
Montreal

THE MONTREAL Medico-Chirurgical Society was founded on Saturday, the 23rd day of September in the year 1843 at a meeting of members of the "Medical Faculty of Montreal", held at the house of Dr. Crawford in little St. James St. It was unanimously resolved by those present, nineteen in number, "That it is very desirable that the members of the Medical Faculty of Montreal should have an opportunity of meeting in a friendly manner for the purpose of communicating together on subjects connected with their profession, and the undersigned agree to form themselves into a Society for that purpose."

The following "fundamental laws" were adopted:

1. It shall be called the Montreal Medico-Chirurgical Society.

2. The objects of the Society shall be the communication of any subject connected with the medical profession, whether in the form of cases in actual practice, details of post-mortem examinations, the exhibition of preparations in morbid anatomy, chemistry, natural history, or any other branch of interest to the profession. (This would justify the problems of medical economics.)

3. It shall be the duty of the president of the evening to maintain order in the Society's proceedings, to read and explain all the motions submitted to him, and carefully to attend to the enforcement of the laws of the Society.

So much for the birth of the Society. Its growth was not always steady, and at one period, from 1852 to 1882, it would appear (as minutes are lacking) that it existed in suspended animation; however, at the end of this period it became robust and in October 1889, application was made to the Mayor and City Council of Montreal for incorporation, the object of this "Social Club" being stated as "the reading and discussion of papers on professional subjects and other matters of medical interest". The Society obtained a seal, began a register of members, and issued certificates of membership.

A review of the problems, frequently recurrent, that have presented themselves to the Society is most interesting and instructive. Attendance, then as now, frequently came up for discussion. As early as the second year of the Society, it is noted that the meeting of June 1, 1844, had to be postponed as there was no quorum (which was set at nine). Worse still, there was no quorum at the annual meeting on September 25, 1849, and it was postponed for two weeks. The minutes of the year 1850 are a repetition of meetings at which there was no quorum and the Society hobbled along. The last entry of March 6, 1852, stated tersely that the Secretary had resigned and a new one had been appointed.

With the resumption of activities in the '80's, attendance was fairly good on the whole, although the entry of April 3, 1885, is somewhat reminiscent of some meetings in our past year: "There were present a very small number (7) owing to the great storm and its being Good Friday."

In the session of '97-'98 there were numerous meetings at which the absence or late arrival of the officers necessitated the nomination of temporary chairmen. In 1900 the attendance problem became so acute that Council was asked to deal with it, after a meeting at which no officers were present and the total attendance was 10. It would appear that we are doing somewhat better at present, for the officers do turn up, as well as several others of the faithful.

On the financial side the Society managed to get by, though at times perilously near to bankruptcy. The Treasurer's report for the first year showed a credit balance of £4/6/– on a basis of 32 members. In 1845 the annual fee was set at 10/– but five years later there were evidently hard times and the fee was reduced to 5/– while an attempt (the result of which was not reported) was made to have the Mechanics Institute reduce the charge for rental of rooms. But the lowest ebb was in 1884, when at the annual meeting it was reported that the balance was $1.89.

Apparently fees were not always paid up, for a motion was passed in 1894 that a list of names of members in arrears should be posted on the bulletin board in the Society's rooms.

The question of quarters for the Society also has had a recurring cycle. In the first years, meetings were held at the homes of the various members, but this soon gave place to meeting in the Society's rooms which sometimes, as now, were obtained for the meeting nights only, but in the '90's and for some time subsequently there were more permanent quarters, with reading room and library, including some of the current journals.

Many of us here will remember some recent studies of the possibility of obtaining a permanent home for the Society; such studies have recurred at several times in the history of the Society and, indeed, in 1896 a committee was formed to decide "the future location of the Society". The report of that committee was a triumph of diplomacy, for its decision was that it was unable to decide. However, this did not kill the idea, and over the next two years several suggestions were made, such as to buy a house and rent the upper floor or to join with the Society of Civil Engineers in joint quarters (and it is of interest that it is not so long ago since we held our meetings in the Engineering Institute of Canada); finally a motion was passed to incorporate and purchase property suitable to the needs of the Society. In consequence of this a committee of three was appointed to act with Council to provide a permanent home for the Society. In preparation for financing it was moved that fees be increased to $15.00 (a tidy sum in 1900) but this was amended and passed at $10.00. The final result was not the purchase of property, but the leasing from the Bank of Montreal of the top floor of the West End Branch,

*Adapted from the address of the retiring President, Montreal Medico-Chirurgical Society, Annual Meeting, May 9, 1958.

which is still at the corner of Mansfield and St. Catherine St. The Society remained there for a number of years, and I am sure that quite a few of our more senior members have, like your retiring President, attended meetings in those quarters.

We still do not own our property, but it would be a safe prediction that the question may well arise again cyclically and in the not too distant future.

The activities of the Society have fallen generally under the headings of scientific presentations, public health problems, and public relations, which became closely intertwined.

At the meetings in the early years, the speaker of the evening was appointed ahead of time and gave a paper on some clinical cases with which he had been concerned. It is of historical interest that at the first meeting in 1843 the presentations were:

1. A Case of Paraplegia, by Dr. Holmes.
2. A Case of Placenta Prævia, by Dr. Bruneau.
3. Demonstration and Distribution of Smallpox Vaccine, by Dr. Fraser.
4. Mental Influences on the Process of Gestation, by Dr. Trusler.

The last paper gave rise to a lengthened "conversation on the physiology of conception and the effect of mental influences on the process of utero-gestation". It would thus appear that the neurological, obstetrical, public health and psychiatric sections had an early germination at this first meeting.

In the '80's the program became more fixed, with the presentation of pathological specimens at first, followed by more formal papers. The name of Dr. Osler appears frequently in these presentations, and in the address of the retiring President in 1884 mention was made of the great loss sustained by the Society in the removal of Dr. Osler to Philadelphia, when he was made an Honorary Member and given an engrossed address.

About this time a case report was presented of children of one family who "interchanged scarlet fever, measles and whooping cough"; an interesting therapeutic note is the exhibition of quinine in whooping cough, with good effect.

The progress of science is evident in the programs of the meetings. On November 21, 1890, a demonstration was given of the staining of sputum for Koch's bacillus (incidentally, I wonder how many of our members could do this today), and letters of introduction were given to Drs. McConnell and Ross on going to Berlin to study Koch's treatment. Transportation must have been more rapid in those days of 1890 than we think, for a report was duly made to the Society by these gentlemen on January 23, 1891.

Possibly our present-day endocrinologists may feel a bit humble to learn that in April 1893 (just 65 years ago) Dr. Blackader presented a case of Addison's disease to which he was giving a new form of treatment, namely the feeding of minced suprarenals. There was no subsequent report, so it is presumed that the treatment was unsuccessful.

But neurosurgeons, bronchoscopists and cardiac surgeons can also share in the humbling process when they hear that in one evening, that of February 9, 1894, Dr. Bell showed two patients, completely recovered, on whom he had operated, one for a compound depressed fracture of the left occipital bone, the other for removal of a bullet which had penetrated the left frontal bone and the brain substance to a depth of two inches. He also showed a third case of a child from whose lower division of the left bronchus he had removed a pencil (after tracheotomy). Not to be outdone, Dr. Shepherd presented a case in which he had removed "without difficulty" two needles from the heart of an alcoholic who had driven them in himself.

But the monster meeting of those days was that of February 7, 1896, when 95 members turned out to see a series of negatives which Professor Cox of McGill had obtained by Roentgen's new method of photography, the most interesting of these being one showing the position of a bullet between the tibia and fibula. The minutes of the meeting end with the note that, owing to the lateness of the hour, the paper of the evening was postponed. In the following August, a special dinner meeting was held in honour of Lord Lister, who was presented with an illuminated address.

And lest we think that the discussions were all on scientific and academic aspects of medicine, I would refer to a meeting in September 1845 at which a tariff committee was appointed and brought in a schedule which was approved in January 1846. Perhaps a short summary of its provisions would be of interest to all of us in these days of inflation.

The 24 hours were divided into three periods:

Day visits	8 a.m.- 8 p.m.
Evening visits	8 p.m.-10 p.m.
Night visits	10 p.m.- 7 a.m.

and patients were divided into first-class and second-class groups according to their financial and social status. As an example, day visits were 5/– for first class and 2/6 for second class, whereas evening visits were 10/– and night £1/5/– for first class, with second class accordingly. A consultation cost £1/5/–, and visit with written advice and certificate, £1 or 10/–. Visits to the country were charged specially– Côte des Neiges 15/–, St. Laurent 30/–, and Beauharnois and St. Anne's £10. Three years later the Society expressed the opinion that in the event of a report to an insurance company, it was only an "act of justice" that a fee should be paid.

The relations of the Society to organized medicine were much more intricate in the early years than they are now. Shortly after the founding, a movement was launched having for its object the formation of a general association of the members of the medical profession of the province, and even further afield; in preparation for this, the "code" was revised to correspond with those of the societies in Quebec City and in Toronto, and delegates were appointed to attend a meeting to plan for such a united association. However, this effort failed and was reported to our Society in these words: "Your delegates feel reluctantly compelled to attribute the event to the conduct of some of the representatives of the Quebec Medical Society, as well as of certain members of this Society who, in raising the question of the right of voting, demonstrated most distinctly and forcibly their determination to exclude your delegates from all participation in the business of the meeting and to treat the Society which they (your delegates) represent with the most bitter contempt."

It would thus appear that it was just as difficult in those days as it is now to persuade a group of

medical men to act together and sink their individual differences.

However, apparently this attempt did some good, as the President in reviewing the work of the year 1847 used these words, "The formation of this [the Medico-Chirurgical] Society led to the formation of another having a still more extended and important sphere of action." He was referring to the recently constituted College of Physicians and Surgeons of the Province of Quebec, with which future relations were not always on such a cordial basis. Thus we find a note in the minutes of December 15, 1893, that there were comments on the laxity with which the C.P.S.P.Q. was run because of poor office work, and in 1898 things had evidently reached such a pass that a committee of the Society was organized to consider the election of proper representatives on the Council of the C.P. and S. in the approaching election and funds were raised for the expenses of this committee. Later reports show that these funds were used to make sure that all members had paid their fees and so were eligible to vote, and that they were aware who was the "proper representative" to vote for.

The question of licensing regulations, then as now, troubled our Society, and we find in the minutes of November 16, 1888, the following resolution, moved by Dr. Roddick and seconded by Dr. Trenholme, that "in the opinion of this Society it is desirable that the Provincial law should be brought into harmony with the Imperial Medical Act of 1886 so far as the latter refers to the colonies." This apparently went further than the motion which had been introduced to endorse the action of the C.P. and S. with regard to reciprocity of degrees with Great Britain.

This idea must have stimulated the vision of a broader registration basis in Canada. At the meeting of March 19, 1899, Dr. Roddick set forth a scheme for an Act of Parliament which would fully deal with the question of "Dominion Registration", which was followed by a motion assuring the support of the Society and expressing hopes for its success.

Possibly stimulated by this action, and also by the request by a physician in Smiths Falls for assistance in defending a suit brought against him for alleged malpractice, a motion was passed that "The time is ripe for the formation of a Dominion Defence Association, and the Society is prepared to support such a move". Incidentally, funds were collected to aid in the defence at Smiths Falls and the case was dismissed.

It would seem to me that we should pause here long enough to realize that our Society was thus to a great extent responsible for both the Medical Council of Canada and the Canadian Medical Protective Association, both of which have proved their worth.

There is also considerable evidence over the years of activity in what is now known as "public relations". The first notation appears in the meeting of January 6, 1844, just three months after the founding of the Society, when there was a presentation and discussion of "two cases of retention of menses, the result of which showed the extreme caution imperatively called for among the members of the profession, in those cases where anomalous symptoms present themselves, with the view to preventing the circulation of false reports, based upon erroneous data, among the community generally." Such a delightfully stated problem in public relations can but cause one to wonder about the gossip circulating in Montreal concerning the two unfortunate subjects of the communication.

Again in 1849 the Society took cognizance of its responsibilities by calling an extraordinary meeting "to allay public alarm and to establish confidence in the measures being undertaken in the prevailing epidemic" (ship fever).

Apparently relations with the press could be troublesome, as evidenced by the note of the meeting of July 6, 1883, where a motion was passed that "The Society should take steps to put down the reporting in the public newspapers of 'fearful operations' performed in our hospitals, together with the names of the operators". Possibly nowdays we have an immunity developed over the years, and take such things for granted, not only locally but also on a national scale. However, I do not think that today there would be any need for a member to "speak strongly", as did Dr. Reed at the following meeting, "of the folly of medical men writing puffs and recommendations for patent medicines of unknown composition".

Again in the next year it was regretted that "a garbled version of the report on the Insane Asylums of the Province had appeared in the daily press, presumably because a member had talked out of turn, an action that was strongly denounced".

In these days of hospital campaigns for funds it is interesting to read that in 1900, when a public appeal was being made on behalf of the Montreal General Hospital, a motion was presented to the Society supporting the appeal but requesting that "the Society should suggest to the Committee of Management of the hospital a measure to popularize the institution among the many medical practitioners of this city not connected with it: viz., that the By-laws be altered so that any member of this Society resident in the city be permitted to treat his own private patients in the medical private wards of the institution, and also to have the privilege of assisting the surgeon who has been called in by said general practitioner to perform any necessary operation or administer the anæsthetic to the patient as they shall agree between the two". This reminds us of our recent meeting when the same subject was discussed in panel form.

There was a vigorous discussion, and further consideration was postponed to the next meeting. The sponsors sent a letter withdrawing the motion, which was not accepted until it was reworded into a "simple letter of withdrawal of the resolution", and so it ended.

While there are numerous other items of public relations, we should not leave out an inquiry from the superintendent of the W.C.T.U. as to the effect of tobacco smoking on the young, which was referred to Dr. Birkett, whose reply I have not found. Perhaps it could be used in the present-day controversy on cigarette smoking.

The Society was most active in matters of public health, and as early as 1847 it pointed out to the civic authorities "the defects in the present system of registration of deaths and the best mode of remedying it in order that the advantages of accurate statistical returns may be available to the profession and the public".

In the '80's, the public health situation was very active, and there was a resolution favouring the founding of a vaccine institute, and a re-endorsement of a motion pointing out the necessity of and en-

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couragement of vaccination, which was to be published in the city press.

For some 10 years there was continued agitation to improve the smallpox hospitals and the sanitary condition of the city in general, some of the motions being so vehement that they were tabled and toned down later before presentation to the civic authorities. In 1892, during a cholera scare, a deputation of the Society met with a group from the Federal Government and were well received, which was used as a lever against the city administrators. It is of interest that one of the proposals was that all victims should be cremated, but as provincial rights appeared here, it required the authority of the legislature, which was not forthcoming.

The occurrence of a typhoid epidemic in 1893 led to prolonged pressure for better control of the milk supply and the appointment of a civic bacteriologist; however, the minutes of the '90's are full of motions on this problem, which was not well stabilized until much later. As a commentary on the situation it is worth noting that in 1898 there was passed a resolution supporting Alderman Ames in his fight to abolish privy pits within the city limits. The century ends with negotiations being carried on for the establishment of an infectious diseases hospital.

A review of this type would not be complete without reference to the problems of membership which have arisen during the life of the Society. As early as 1851 a motion to admit students was defeated but at a later date, 1889, the resident staff of the Montreal hospitals were admitted as temporary members.

About this time the "junior members" of the Society made various bids for autonomy or at least one meeting "apart", but this was viewed as a step leading to secession "which would be detrimental not only to the Society itself, but also to the individual members and especially the younger members". However, a *modus vivendi* was developed and no small or splinter group was formed. Apparently similar ideas were held when the specialty groups were formed within the ægis of the Society at a later date.

But the Society was really shaken when in April of 1898 an inquiry was received from Dr. Grace Ritchie England concerning the admission of women to membership. It was explained that Section A of By-Law 1 prohibited this. A gallant member immediately gave notice of motion to change the word "man" in this by-law to "practitioner", thereby making the requirement for membership read "duly qualified medical practitioner in good standing".

Whether as a deliberate act of propaganda or not, in the meantime the paper of Dr. Maude Abbott on functional heart murmurs had been read to the Society by Dr. Stewart and was "enthusiastically received", and when the motion of amendment was presented on December 1, 1899, it was passed by a vote of 29 to 4. It is of interest that the first women members were Dr. Abbott and Dr. Elizabeth Mitchell, elected January 1899, but it was not until October of 1899 that the instigator of this change was elected.

There is still another heading of the Society's activities, namely that of conviviality, and I would like to refer to two such occasions. The first is best reported in the words of the secretary as set forth in the minutes of the meeting of December 29, 1882:

"The remainder of the evening was passed in a very happy manner after the good things were duly disposed of. Amusing incidents in the experience of the members were related, and after songs from several of those present, the meeting was finally adjourned with the congratulations of the chairman on the complete success of the entertainment and the suggestion that such reunions could not be repeated too often."

The second outstanding event was the 50th Anniversary dinner which was held in the Windsor Hotel on November 22, 1893. Members of the Gastro-Enterological Section should be particularly interested in the menu which can best be described as terrific, from the start with oysters on the half shell to the end with a demi-tasse. The toast list was also formidable and it is to be hoped that the speeches were short. Starting with a toast to the Queen, there followed toasts to the Governor General, the Mayor, the Medico-Chi, La Société de Médecine Pratique, the guests, the ladies, and the press. It is stated that the President, Dr. Bell, referred briefly to the history of the Society. The toast to the press must have been effective, for the *Gazette* of the next day had a full report, from which I quote the following:

"The doctor manages to enjoy himself thoroughly when he throws aside his dignity and professional air —songs and jokes with a modicum of speech-making after a most sumptuous repast made the time fly merrily."

As one who has acted many times as treasurer of medical groups' dinners, I cannot leave this event without reporting the financial side. There were 54 present and the total expenditure was $199.15 with receipts of $171.00. It was consequently necessary to assess the sum of $1.25 each against the signers of the guarantee fund.

And now I think that most of you will agree that my text has been well chosen, and really no new things have developed over the now almost 115 years since the founding of our Society; but in closing, I cannot resist the temptation to be the Devil's Advocate. Perhaps there *are* some new things under the sun.

Early in my researches I was struck by a report of a meeting in 1848 at which the doctor chosen to present the discussion of the evening arrived late with the excuse that he had been delayed because he had been visiting a patient who had just died, the third child of one of their colleagues to succumb to malignant scarlet fever, which had "defied treatment"! There was considerable discussion and the meeting finally adjourned "with the conviction of the inadequacy of our means to combat those terrific cases which in fatality scarcely yield to the plague".

Again at the meeting of February 9, 1894, almost 50 years later, there was a lengthy discussion of the severity of the epidemic of scarlet fever prevailing in the city, and it was pointed out that the city should provide further accommodation for the isolation of patients suffering from this disease. I think that it will come as a surprise to most of us here to learn that according to the statistics of the Mount Royal Cemetery Company, which were kindly furnished to me by Mr. Wallace Roy, 12.3% of the total burials in that cemetery in that year of 1894 were of victims of scarlet fever.

And then some 20 years ago came the sulfonamides, followed by penicillin and the other antibiotics, and it

would seem that the prayer of those who were at the meeting in 1848 for an adequate tool of treatment had been answered. Today we are looking for patients to place in our isolation hospitals and having difficulty in finding a case of scarlet fever to show to our students, instead of seeking for more beds as in 1894. Perhaps this *is* something new under the sun.

And so, if I have not justified and sustained my original text, I must perforce in conclusion replace it with another, and with it, I am sure, you will all agree. It is found in the sixth chapter of the Book of Genesis, at the fourth verse, and reads:

"And there were Giants in the Earth in those Days."

Association Notes

CANADIAN COUNCIL ON HOSPITAL ACCREDITATION

The program of the newly formed Canadian Council on Hospital Accreditation (Conseil canadien d'accréditation des hôpitaux) was formally inaugurated at C.M.A. House on Saturday, January 17, with Dr. E. Thibault in the chair. The ceremony followed a two-day meeting of the Council, and a luncheon at the York Club, at which the speaker was the Hon. J. Waldo Monteith, Minister of National Health and Welfare.

Mr. Monteith, in congratulating those responsible for the new program, said:

"I appreciated being invited to these meetings. It was a generous gesture on your part. But I would like to think it was more than a gesture. I would like to think – and I am sure I am correct in doing so – that your invitation reflects the sense of partnership achieved in Canada between government and private agencies in the health field.

"While only logical, such co-operation is far from automatic. As we all know, it has to be worked at in small things and in large. But the rewards are more than worth the effort – as witness the way in which government, organized medicine and hospitals have joined forces in bringing the new hospital insurance plan into operation. Without doubt, this most complicated project could not even have been attempted but for the mutual trust and understanding built up over the years by the various branches of our health team. . . .

"The program's achievements are important. But no less important is the way in which it has been carried out. This has not been something imposed from above by government or any other authority. Hospital accreditation has been a spontaneous effort on the part of the medical profession and hospitals to put their own houses in order – to set their own ideals of service and efficiency and to translate these into practice. They have been their own conscience and watchdog. They have asked for no financial assistance from any quarter. Theirs has been an exercise in self-discipline which could well commend itself to professional groups everywhere.

"In the tradition of Canadian life, governments have welcomed this development with open arms. Not only have they had no desire to get involved in accreditation, but they have realized that the work itself could best be done independently by those who furnish the services designed for improvement. This has certainly been the view of federal authorities and has, I believe, been fully justified by the results achieved."

Alex Gray, Toronto

The charter of the Canadian Council on Hospital Accreditation is being examined by the Hon. J. Waldo Monteith, Minister of National Health and Welfare, Ottawa; Dr. John I. Brewer, Chicago, Chairman, Joint Commission; and Dr. A. L. Chute, Toronto, chairman of the Council.

After paying a tribute to previous U.S.-Canadian co-operation in this field, Mr. Monteith continued:

"The introduction of hospital accreditation on a purely Canadian basis is timely on another ground. As I hardly need remind you, it coincides more or less with the start of the new hospital insurance scheme across the country. In fact, this plan went into force in a sixth and seventh province – Ontario and Nova Scotia – on the very day that the accreditation program became effective.

"What is the relation between these two historic undertakings? This, I suggest, can best be seen by noting one of the major emphases of the hospital insurance plan. I am thinking of its stress on improving standards of performance in hospitals. We in government do not view the insurance plan as merely a fiscal project – simply a new method of paying for hospital care. We regard it primarily as a service program which should promote increasingly better quality and efficiency of the whole gamut of procedures centred in hospitals. We look at it as basically a health project which has the well-being of the individual patient as its prime objective. In other words, the plan is directed towards the same goal as has been set for the new all-Canadian accreditation program.

"For our part, we have seen to it that the insurance program itself will foster the continuing improvement of hospital care. Special machinery has been built into provincial plans for this very purpose. But this machinery cannot do the whole job. A good deal of responsibility must still rest with the medical profession and hospitals. In fact, experience shows that quality of care can best be ensured by doctors and hospital authorities working together. This is essentially a professional matter, which should be handled as such. The onset of public hospital insurance in no

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way changes the situation. Governments are not going to dictate rules of procedure. While standing ready to provide technical advice on certain hospital problems, they look to the medical profession and hospital administrators to bear the brunt of this important activity.

"It is obvious to me that what has already been done in the way of hospital accreditation has eased the introduction of the hospital insurance plan. Indeed, had it not been for this voluntary effort, the plan would face much greater problems in achieving efficiency of operation. Now that the insurance program is actually functioning, accreditation will assume an even larger significance. As an independent stimulus to good hospital practice, it will serve as a key support to the program's orderly and effective development.

"In turn, progress in accreditation should be reinforced by the insurance scheme's impact on hospital financing. Since these institutions will no longer have to operate in the red, resources should be available to enable and encourage more and more of them to meet accreditation standards.

"Frankly, it is in connection with the hospital insurance plan that I see the greatest significance of the new all-Canadian accreditation program. The insurance plan is a distinctly Canadian project, tailored to our own needs and conditions. It already has emphases — and no doubt will develop more — which are unique as compared with arrangements in other countries, including the United States. This being the case, it is obviously important that our accreditation activities should be equally Canadian in their approach and responsive to these special trends.

"As an example of the latter, I might mention the insurance scheme's stress on long-term care — the gearing of length of stay in hospital to medical necessity. Here is an area where the Canadian Council on Hospital Accreditation might well examine the realism of existing criteria. Among other things, it might ask itself whether further attention needs to be given to encouraging accreditation of chronic hospitals."

After a brief review of the health insurance program, Mr. Monteith recalled that last June, at Halifax,

Alex Gray, Toronto

Field representatives of the Canadian Council on Hospital Accreditation (left to right): Dr. K. E. Hollis, Toronto; Dr. D. D. Campbell, Hamilton; Dr. J. J. Laurier, Montreal; Dr. Marcel Langlois, Quebec; Dr. A. L. Swanson, Saskatoon; and Dr. F. C. Bell, Vancouver. Dr. W. I. Taylor, Toronto, Secretary and Executive Director of the Council, is at the extreme right.

Alex Gray, Toronto

Chatting after the inauguration ceremony are (left to right): Dr. D. F. W. Porter, Vallée Lourdes, N.B., President, Canadian Hospital Association; Dr. A. F. VanWart, Fredericton, President, Canadian Medical Association; Dr. R. M. Janes, Toronto, Past President, Royal College of Physicians and Surgeons of Canada; and Dr. Pierre Smith, Montreal, Public Relations Officer, L'Association des Médecins de Langue Française du Canada.

he challenged the medical profession to a leadership role in the insurance plan. He thought that in the intervening six months it had accepted that challenge.

The inauguration began with a welcome to the guests by Dr. Thibault, who expressed his view that this was a historic occasion for Canadian hospitals. This did not mean a total separation from the United States in the hospital world, for the married daughter would return to her mother's house from time to time. He stressed the value to Canadian unity of the good relationships between the two great ethnic groups involved in this work, and pointed out that it was the duty of hospital accreditation authorities to attend to both the bodies and the souls committed to their care. He then presented a gavel to Dr. A. L. Chute, the incoming chairman, who introduced the officers for 1959, including the vice-chairman, Mr. J. E. Robinson, the treasurer, Dr. J. B. Neilson, and the secretary, Dr. W. I. Taylor.

Father Hector Bertrand, S.J., asked a blessing for the future work of the Council. Mr. W. G. Tucker, Q.C., (Solicitor to Council) presented the charter and seal of the new Corporation to the incoming chairman, Dr. A. L. Chute.

The guest speaker was Dr. E. Kirk Lyon, referred to by Dr. Chute as "Mr. Accreditation". Dr. Lyon described the development and significance of the new program, tracing it from the inauguration of a standardization program 45 years ago by the American College of Surgeons. The first A.C.S. survey revealed results so bad that the records were burned. Only 12% of hospitals could at first be approved.

The program was at first entirely a voluntary effort by the American College of Surgeons, who financed it for many years themselves. In 1950, all resources in Canada were pooled with representation from the C.M.A., the Royal College of Physicians and Surgeons and other bodies to consider a Canadian program. Soon afterward the A.C.S. gave notice that it could no longer carry on a program, and eventually the Joint Commission on Accreditation of Hospitals replaced

it, while almost concurrently a Canadian commission was formed in this country.

Dr. Lyon noted how the Canadian Commission had raised standards of hospital construction, records, diet, and medical care, and done much to stamp out unnecessary surgery and dichotomy; he emphasized the absolute necessity for close co-operation between hospital and medical authorities. He considered that such an independent body as the new Canadian Council could perform the task of accreditation better than a provincial government commission, and was glad to have the assurances from government that they would not interfere with its work.

He wanted to see better guidance given to medical departments as well as to surgical ones. A patient could be just as dead from a badly managed coronary attack or diabetic coma as from a badly executed operation or badly administered anæsthestic. He trusted that the U.S. Joint Commission and the Canadian Council would go forward, each respecting the sovereignty of the other and striving together for the common good.

The responsibility for accrediting Canadian hospitals was then formally handed over by Dr. J. I. Brewer, Chairman of the Joint Commission on Accreditation of Hospitals. Greetings to the new Council were extended by the director of the American Hospital Association, Dr. Edwin L. Crosby; the president of the Canadian Hospital Association, Dr. D. F. W. Porter; the president of the Canadian Medical Association, Dr. A. F. VanWart; the past president of the Royal College of Physicians and Surgeons of Canada, Dr. R. M. Janes; and the public relations officer of L'Association des Médecins de Langue Française du Canada, Dr. Pierre Smith.

Dr. VanWart said, in part:

"The timing of this inauguration is most opportune. This year many of the provinces are entering the field of hospital insurance plans. It is to the credit of all our governments that they have left the Boards of Management of our hospitals in the hands of local citizens. Service on hospital boards has attracted public-spirited business men, and they have been responsible for the advancement and present status of our hospitals. Governments, as they pour more money into our hospitals, will require adequate inspection of hospitals. If our inspections are not thorough, they will replace our Council with their own inspection boards and these boards will regulate the hospitals. It behoves us to see that this new and truly Canadian Council on Hospital Accreditation becomes so efficient that governments will recognize it as their medium of hospital inspection. If this is accomplished, then with the co-operation of the lay hospital boards we should have continuous improvement of hospital services."

The members' representatives to Council will be:

Canadian Hospital Association: Dr. A. M. Clarke, Rev. A. L. M. Davis, O.M.I., Dr. Gérald La Salle, Dr. J. B. Neilson and Mr. J. E. Robinson

Canadian Medical Association: Dr. E. Kirk Lyon, Dr. N. N. Levinne, Dr. B. H. McNeel and Dr. D. A. Thompson.

Royal College of Physicians and Surgeons of Canada: Dr. A. L. Chute and Dr. W. Keith Welsh.

L'Association des Médecins de Langue Française du Canada: Dr. Eugène Thibault.

MEDICAL MEETINGS

THE CANADIAN SOCIETY FOR CLINICAL INVESTIGATION

The Canadian Society for Clinical Investigation held its scientific program and business meeting on January 22, 1959, in the Amphitheatre of the University of British Columbia Faculty of Medicine Building, Vancouver, B.C. In the morning session, guests were welcomed by Dr. H. W. McIntosh.

The session began with a paper on patterns of infection with enteroviruses by Dr. D. M. McLean of Toronto, who described experience in that city and elsewhere. He pointed out that very few of the so-called non-paralytic "polio" cases in Toronto were associated with poliovirus. Thus for example up to 1955, out of 96 cases of this condition, better termed aseptic meningitis, 18 were due to Coxsackie B infection. In 1955, Echo virus was found and in 1958 a special strain of Coxsackie virus known as B_5. He noted that 1958 experience in Toronto showed a wide variation in the syndromes produced by a single type of virus; it was very uncommon to find a healthy and asymptomatic person harbouring enteroviruses. A new phenomenon had been the appearance of a pericarditis in children, whose distinguishing feature was that they did not seem so ill as patients with rheumatic pericarditis.

Dr. H. E. Taylor of Vancouver discussed the pathological effects of lathyrogenic compounds on the maturation of epiphyseal cartilage. Rats were given lathyrogenic compounds such as BAPN (beta-aminopropionitrile), beta-mercaptoethylamine, and semicarbazide. These caused a marked widening and softening of the epiphyseal cartilage with subsequent slipping of the epiphysis and deformities such as kypho-scoliosis. There were however individual differences in action; BAPN did not cause scoliosis, and the mercaptoethylamine inhibited growth but only when given in the diet. Moreover, BAPN and semicarbazide blocked cell maturation in the zone of maturing cartilage cells, while the third compound blocked maturation at the zone of proliferating cells.

Dr. Huntington Sheldon of Johns Hopkins University described observations made with the light and electron microscope, tissue culture and biochemical methods on bone in experimental rickets induced in rats by vitamin D deficiency and a low phosphate diet. It seemed as if the osteoblast acted as a kind of membrane through which substances must pass before they become collagen, which was secreted in an afibrillary form and polymerized to the recognizable form.

Dr. D. Fraser of Toronto discussed the simple form of rickets refractory to vitamin D, with special reference to two cases in which this type of rickets was associated with hypophosphatæmia but not (as had been thought formerly) with renal functional disturbance. He refuted the theory that this condition was associated with a primary abnormality in function of the renal tubules. He thought that the characteristic excessive renal clearance of phosphorus in this disease was the result of secondary hyperparathyroidism.

Dr. Duncan McPherson of Vancouver had studied continuous intravenous infusion of calcium gluconate in eight adult male patients, five of whom were normal and three suffering from Paget's disease. When

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10 mg. per kg. body weight was given in one hour, the rise in plasma calcium level was less than expected, indicating a wholesale storage of calcium in the skeleton. It seems that the skeleton may act as a calcium reservoir, holding 50 to 100 mg. per kg. available for exchange. In Paget's disease there is a high bone blood flow with an abnormally large skeletal pool. Urine calcium in cases of Paget's disease was much below the normal range after the infusion.

Dr. Zipursky of Winnipeg had studied seven cases of congenital non-spherocytic hæmolytic anæmia occurring in three families, with variations between a mild anæmia and a severe uncompensated form. In one child aplastic crises occurred, possibly infective and requiring transfusion. Severe anæmic episodes were also seen as the result of bone marrow failure. It seemed as if intravascular hæmolysis might occur, associated with an inherited shortening of the life span of the red blood cell.

Dr. J. F. Mustard of Toronto described the effect on blood clotting of intravenous injection of phosphatidyl ethanolamine and phosphatidyl serine. Injecting the former phospholipid accelerated the blood thromboplastin mechanism whereas phosphatidyl serine had an anticoagulant action, this effect being partly against Christmas factor activity. Administration of enough phosphatidyl serine before phosphatidyl ethanolamine blocked the action of the latter in blood clotting. Confusion in some clotting studies might be partly due to changes in phospholipids.

Dr. P. Constantinides of Vancouver described studies with intravenous injection of Paritol-C, an analogue of heparin and a sulfated polysaccharide with a mannuronic acid repeat unit. Given intravenously in nine cases of hypercholesterolæmia and hyperlipæmia for five days twice a day in a dose of 5 mg. per kg. per day, it restored elevated total serum lipid levels to normal and suppressed postprandial lipæmic turbidity. In five cases it restored the elevated serum cholesterol to normal within 72 to 96 hours. In seven patients it appeared to cause clinical improvement. No serious toxicity was detected and the drug appeared a promising agent.

Dr. L. G. Israels of Winnipeg described four cases of an unusual type of jaundice occurring in two Mennonite families in Southern Manitoba, living a few miles apart and not related. The jaundice was associated with a hyperbilirubinæmia not related to breakdown of circulating red cells or to defect in liver function. The primary overproduction of bilirubin has been termed "shunt hyperbilirubinæmia". Jaundice and splenomegaly appeared in early adult life, and the excess bilirubin appeared to arise from marrow erythrocytes or their precursors. The serum bilirubin was predominantly of indirect reaction, and red cell survival somewhat short. Hæmolysis when present was corrected by splenectomy, which, however, did not affect reticulocytosis, normoblastic hyperplasia of marrow, hyperbilirubinæmia or increased urobilinogen excretion.

Afternoon Session

The afternoon session began with a short business meeting at which the following officers were elected: *President*, Dr. J. C. Beck, Montreal; *Vice-President*, Dr. Fernand Grégoire, Montreal. *Council:* Dr. M. H. Darrach, Vancouver; Dr. D. Wilson, Edmonton; Dr. E. M. Nanson, Saskatoon; Dr. John Gemmell, Winnipeg; Dr. N. M. Lefcoe, London, Ontario; Dr. M. Ogryzlo and Dr. R. Slater, Toronto; Dr. Garfield Kelly, Kingston; Dr. D. V. Bates, Dr. J. C. Beck and Dr. F. Grégoire, Montreal; Dr. Gaston Sauvé, Ottawa; Dr. Jean-Marie Delâge, Quebec; and Dr. W. I. Morse, Halifax, N.S.

The membership of the Society now exceeds 200; 60 applications have been received since last year's meeting, of which 32 have been accepted and 28 are still being processed.

Scientific Session (Afternoon)

Dr. Eleanor McGarry of Montreal described studies on the use of anterior pituitary hormones as antigens. The purposes of the studies were (1) to attempt to produce antibodies to anterior pituitary hormones; (2) to explore their specificity; (3) to use them as indicators for identification and measurement of the hormones in body fluids. She found it possible to produce antibodies to anterior pituitary hormones in all animals tested and showed that growth hormone was species specific whereas ACTH was not.

Dr. E. H. Venning of Montreal described the secretion of various steroids by human adrenal cortex, as measured *in vitro* on adrenal glands obtained from 12 adult patients with adrenal hyperplasia (nine with Cushing's syndrome, three with virilization). The adrenals from both groups of patients secreted the same steroids, with hydrocortisone as the main constituent but with lower values for hydrocortisone and cortisone in the patients with virilization than in Cushing's syndrome. *In vitro* output from the glands was considerably less than average daily urinary excretion *in vivo*, though glandular and urinary levels were roughly parallel. Women with Cushing's syndrome had a lower ratio of urinary 17-ketosteroids to 17-hydroxycorticosteroids than those with the virilizing syndrome. It seems that the different clinical picture in these two types of adrenal hyperfunction may be associated with a changed metabolism of corticosteroids, with increased production of 17-ketosteroids in virilizing syndrome.

Dr. J. C. Laidlaw of Toronto discussed the effects of œstrogen and progesterone on secretion, disposition and the biological activity of hydrocortisone. His experiments were designed to determine whether the changes in hydrocortisone during pregnancy related to increased secretion of the female sex hormones. These hormones were given to Addisonian patients also given intravenous hydrocortisone, and to normal subjects given intravenous ACTH. Results show that œstrogen administration did not increase hydrocortisone secretion, and that the disposition of this latter hormone was the same as in pregnancy. Progesterone did not affect hydrocortisone, and it is concluded that the changes in disposition of the latter hormone in pregnancy are mostly due to increased œstrogen secretion.

Dr. W. H. Chase of Vancouver had studied the fine structure of normal and stimulated mouse thyroid gland prepared by freezing and drying. Electron microscopy revealed a vacuolar structure in cytoplasm and nuclei of follicle cells, and of the colloid of the follicle vesicle. Stimulation with TSH led to appearance of numerous droplets in the cytoplasm and other changes. Certain changes in the development of the droplets were also described.

Dr. W. I. Morse of Halifax, N.S., gave an account of glucose tolerance studies in nine chronically obese persons and nine controls. With an oral glucose tolerance test, the mean blood sugar values were statistically significantly different in the obese and in the normals. Intravenous injection of glucose (19 g. per sq. metre over 8 min.) gave results not significantly different in the two groups. A glucose utilization index was derived, and it seemed that impaired glucose removal was not an adequate explanation for the results of the oral tolerance test.

Dr. R. J. Slater of Toronto described an unusual case of chronic hypokalæmia associated with renal tubular degeneration, in a nine-year-old boy who had suffered from polydipsia, polyuria, a craving for salt, and generalized weakness. The complete work-up of the case, including bio-assay of an adrenal, revealed a mixture of findings not compatible entirely with the diagnosis either of primary aldosteronism or of chronic inflammatory potassium-losing renal disease.

Dr. J. D. E. Price of Vancouver made a plea for the use of rectal carboxylic acid resins in control of hyperkalæmia. At the Vancouver General Hospital 17 patients (13 with acute and four with chronic renal failure) had been treated with these resins and in seven cases the rectal route had been used. It proved as effective as the oral route for removing potassium and was less irritating and unpleasant to the patient.

Dr. H. Cross of Kingston, Ont., discussed the effect of a large and rapid infusion of magnesium sulfate in patients with raised and with normal blood pressure. Most hypertensive persons responded with a temporary fall in blood pressure, whereas normal subjects made no response. The transient fall in blood pressure returned to the baseline even while there was still a high serum magnesium. There was no significant difference between the hypertensives and the normals as regards excretion of calcium, phosphorus, chloride or sodium but the hypertensives excreted more potassium and had a greater glomerular filtration rate and renal plasma flow.

Dr. A. S. V. Burgen of Montreal had studied the fate of a recently available radioactive magnesium compound, Mg^{28}, injected intravenously in a dose of 8 to 10 microcuries into normal and diabetic patients. There was at first a rapid urinary excretion and a high plasma concentration which gave place to a slower excretion. Roughly one-quarter of the exchangeable magnesium was in a rapidly exchangeable pool. Very little of the Mg in the body was in the plasma or interstitial water. The site of the rapidly exchangeable Mg was unknown; maybe it lay in a complex in collagen or in bone. The slowly exchangeable Mg must be in skeletal muscle or bone. The serum Mg was a poor indicator of total Mg in the body. In diabetics, the only difference from normal was in the wide range of values obtained.

Annual Dinner

The Annual Dinner of the Canadian Society for Clinical Investigation was held at the University Club, Vancouver, on the evening of January 22, with Dr. J. C. Beck of Montreal in the chair.

ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

The Royal College of Physicians and Surgeons of Canada held its 28th Annual Meeting at the Hotel Vancouver, Vancouver, B.C., on Friday and Saturday, January 23 and 24, 1959. The meeting followed the usual pattern. On Friday morning, there were meetings of the divisions of medicine and surgery; on Friday afternoon, the division of medicine continued its session while the division of surgery split into two sections (orthopædic surgery and chest surgery). Simultaneously, the section of obstetrics and gynæcology was holding a panel discussion on perinatal mortality — its definition and problems, with Dr. F. E. Bryans of Vancouver as moderator. On Saturday morning the divisions of medicine and of surgery met, the latter holding its session in the Faculty of Medicine Building of the Vancouver General Hospital. The section of obstetrics and gynæcology also held a scientific session. On Saturday afternoon there was a scientific meeting, followed by convocation, the president's reception and the annual dinner. The annual business meeting of the College was held at the end of the Friday scientific sessions.

Division of Medicine

Dr. Bernard I. Lewis of Palo Alto, California reviewed the hyperventilation syndrome in the light of 250 patients he had seen. In 70% of these the cause was psychological, in 28% it was mixed and in 2% it was purely organic. There was a great preponderance of females in the first group and over half of them had some involvement of the cardiovascular system. The common denominator in symptomatology was overbreathing without the patient's awareness of this, and with acute exacerbations. In these episodes the pCO_2 falls sharply and the arterial pH rises. The manifold symptoms appearing often lead to misdiagnosis; in fact, only one out of the first 50 patients in this series was correctly diagnosed at first. ECG changes were not uncommon. At least 75% of these cases can be cured by the average physician, if he will get the patient to re-create an episode in his office and then abolish the symptoms by having the patient rebreathe into a paper bag.

Dr. H. T. G. Strawbridge of Winnipeg described his experiments on production of chronic pulmonary emphysema. He had produced ischæmia of the lung by repeated intravenous injection of a dyestuff, Caledon blue R.C., into rabbits. He regarded emphysema as a non-specific response of lung tissue to a variety of stimuli, with ischæmic atrophy of the alveolar walls as the basic feature.

Dr. N. M. Lefcoe of London, Ont., took a contrary view on the etiology of emphysema, in discussing the radiological diagnosis of this condition. In 130 patients a chest radiograph was taken and on the same day pulmonary function was tested. The radiologist was asked to classify his films as no emphysema, definite emphysema, and possible emphysema. The timed vital capacity correlated well with the radiologist's assessment, for in cases where the T.V.C. was less than 58% in the first second, the great majority had been pronounced emphysematous by the radiologist. However, the presence of a contracting lesion in the lung appeared to destroy this correlation.

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Dr. J. L. McCallum, Montreal, reported studies on 30 employees of the Montreal General Hospital who had a respiratory infection and who underwent a series of examinations designed to elicit the causative organism. The illness was not severe enough for admission to hospital, but sufficient for ceasing work. Symptoms and signs were inconstant, and radiographs often negative. Only four had a positive throat culture for bacteria. In the 13 cases in which a causative agent was demonstrated, three had a bacterial, seven a virus and three a combined infection. Serology was more reliable than virus isolation.

Dr. J. F. Mustard of Toronto, the 1958 medallist in medicine, summarized a study of relationship between lipids, blood coagulation and atherosclerosis in human subjects and experimental animals. These studies have been reported in the *Canadian Medical Association Journal.*

Dr. E. R. Yendt of Toronto described the experience gained in diagnosis and treatment of 20 cases of renal hypertension seen at the Toronto General Hospital in the past three years. Most of these cases were due to impairment of the arterial blood supply to one or both kidneys. Investigation was difficult, for 13 patients had no symptoms of urinary disease and intravenous pyelography was negative in seven cases. Aortography was unsuitable for screening large numbers of patients, and should be done only if other studies suggested a renal origin for the hypertension. Differential renal function studies were valuable, the volume and sodium concentration of urine specimens collected simultaneously from the two kidneys being determined. Thus in cases of renal arterial disease, there was at least 50% difference in volume of urine secreted by the two kidneys and at least 15% difference in sodium concentration; it was surprising to find this also in three cases of bilateral disease. The author drew attention to the fact that in two out of three cases of stenosis of the renal artery, a loud systolic bruit was heard over the abdomen and costovertebral angle.

Dr. A. E. Thomson of Winnipeg had treated 68 cases of acute renal failure due to such causes as intravascular hæmolysis, major surgery, the triad of trauma, crush and burns, nephrotoxins and water and salt loss. He stressed the value of adrenergic blocking agents such as Dibenzyline in the early phase of failure, and mentioned the problem of potassium intoxication, particularly in the trauma-crush-burn group. The 30% mortality was largely due to a secondary infection; in survivors, renal function was adequately restored.

Dr. D. M. Whitelaw of Vancouver described a case of megaloblastic anæmia due to isolated failure of absorption of vitamin B_{12} in the presence of intrinsic factor. Two members of the family showed the same defect.

Dr. R. B. Goldbloom of Montreal presented a study of tocopherol deficiency in infants and children.

Dr. R. C. Dickson reported a three-year study of the use of potassium perchlorate as a thyroid depressant in hyperthyroidism, or for angina in euthyroid patients. A single dose of 200 mg. had a blocking effect for 24 hours on normal persons but a lesser effect in hyperthyroidism. Dosage of 200 mg. five times a day over eight weeks rendered the average hyperthyroid person euthyroid. Toxic effects were few. The drug was also of value in diagnosis of Hashimoto's disease.

According to Dr. Hamish McIntosh of Vancouver, hyperparathyroidism (H) is by no means rare but the diagnosis is often missed. It may be hard to discover the tumour, which may be extremely small; the most fruitful cases for a search for H are those of recurrent renal calculi. Neither serum calcium nor urine calcium determinations are reliable in diagnosis of H. The intravenous infusion of 15 mg. calcium per kg. over four hours with determinations of serum phosphorus and urine phosphorus has proved helpful. In the normal person, serum P rises and urine P falls; in H there is no rise in serum P.

Dr. W. I. Morse of Halifax, N.S., presented observations on a patient in whom abdominal injury had led to resection of all the small intestine except three feet of jejunum. After the operation he lost much weight and suffered from tetany and convulsions. Seven months after the injury the jejuno-colic anastomosis was undone, a blind pouch eliminated, and all the remaining small and large bowel exposed to the intestinal contents. Weight was gained, and serum calcium and phosphorus values returned to normal. Biochemical findings were reported in detail.

Dr. C. B. Rich of Edmonton had studied 50 cases of mitral stenosis simultaneously by phonocardiography, tracing of left atrial pressure curves and electrocardiography. He detailed the findings in these cases.

Dr. L. DeW. Wilcox of London, Ont., described the diagnostic and therapeutic considerations in cases of symmetrical gangrene of the toes and fingers complicating myocardial infarction.

Describing the principal features of Wilson's disease or hepato-lenticular degeneration, Dr. J. A. Dauphinee of Toronto pointed to the excessive deposition of copper in the brain and liver and in the corneal margin, where it appeared as the Kayser-Fleischer rings. The liver seemed unable to synthesize ceruloplasmin. Chelating agents removed the excessive copper from the tissue in a form excretable in the urine. He described two cases, one of which had been mistaken for some time for Parkinson's disease. Penicillamine had given good results, with gradual improvement over a long period. The improvement in mental state was particularly gratifying. Penicillamine appeared to be more effective than BAL in removing copper. It was probably necessary to continue the drug indefinitely, and this might deplete the body of other essential trace metals such as cobalt. Studies were in progress on this point. He urged physicians confronted with a doubtful case of Parkinsonism to examine the eyes with the slit lamp; the diagnosis could be settled by the biochemist.

Dr. E. E. Daniel of Vancouver had recorded the electrical activity of the small intestine, both in patients with ileal bladders and at laparotomy and in dogs. The slow waves recorded had different frequencies at different levels; the rate fell as the intestine was descended. In the ileum it was 4-7 per minute; in the duodenum it was 8-12 per minute. Fast action potentials were associated with visible contractions. Propulsion and electrical activity had been simultaneously recorded in dogs with balloons. Surgical procedures had no effect on this electrical activity. The slow wave rate was apparently not determined by a pacemaker but intrinsic in the intestine with its origin near the muscle layers. All intestinal

muscle cells seem to possess an electrical activity. Lowering body temperature slowed up all frequencies, which disappeared at 26° C.

Dr. S. Segal of Vancouver presented observations on diagnosis and incidence of hæmolytic disease of the newborn due to ABO iso-immunization. He pointed out that this was probably commoner than Rh immunization but usually mild. A small proportion of infants born of a heterospecific pregnancy developed hæmolytic disease, and in nearly all of these the mother was of group O and the infant of A or B. There were two difficulties in establishing incidence of this condition; one was that many mild cases shade off into early physiological jaundice and the other was that maternal iso-antibodies lack the pathological significance attached to Rh antibodies and the direct antiglobulin test is often negative. He had calculated that the disease probably occurred in about 2.2% of all pregnancies and in 11.1% of "dangerous" matings, when the mother belonged to group O and the father had an A_1 or B agglutinogen or both.

Dr. J. B. Dossetor of Montreal described the medical aspects of management of the first successful renal transplantation in Canada, performed in identical twins. The 15-year-old identical twin girl was admitted with epileptic seizures, papillœdema, a raised blood pressure and albuminuria, and a diagnosis was made of irreversible bilateral chronic pyelonephritis. It was first established that the other twin had a normal urinary tract, and then that the twins were identical (by skin grafting, blood grouping and examination by a geneticist). The legal situation was explored and found satisfactory and after seven weeks of pre-operative preparation to control the blood pressure, the patient was operated upon while in a critically ill condition. The donor kidney was placed in the right iliac fossa and a rapid urine secretion began almost immediately after it had been sutured in place. The blood pressure fell to just above normal after operation and the NPN dropped within 24 hours from 170 to 60 mg. %. Five months later a bilateral nephrectomy was undertaken. In the meanwhile another episode of azotæmia had occurred in spite of apparently good renal function. By the end of the sixth week after the first operation, the patient was well, ambulant and symptom-free.

Dr. R. S. Fraser of Edmonton described follow-up studies on 25 patients who had undergone open-heart surgery. These were the survivors out of a group of 42 patients operated upon, and all the survivors without exception had improved clinically. He described the ECG findings before and after operation, and also the cardiac catheterization findings. He felt that postoperative catheterization in such patients was at present essential if results were to be properly studied. He hoped that further series correlating these findings with the clinical and ECG results would lead eventually to avoidance of the need for re-catheterization.

Dr. P. Constantinides of Vancouver had performed experiments on rabbits in coma in which he had induced atheroma by cholesterol feeding and then either (1) completely withdrawn cholesterol, (2) given an œstrogen (stilbœstrol), (3) starved the animal, (4) given an unsaturated fatty acid, methyl linoleate, or (5) given an inhibitor of cholesterol metabolism in the form of vanadium sulfate. His studies showed that only stilbœstrol had any effect on arresting the progress of atheroma, but unfortunately in half the animals it caused jaundice and liver cirrhosis. Linoleate had a partial effect; vanadium and starvation had no effect.

Dr. D. Bowers of Kelowna, B.C., had traced 33 members of a family in which 31 (spread over six generations) had the characteristics of Marfan's syndrome and two the characteristics of Weill-Marchesani syndrome. Persons with Marfan's syndrome are tall and thin, with spidery fingers and often with aortic disease, while the W-M syndrome is characterized by short stocky build, a brachycephaly and short stubby fingers. In both syndromes dislocation of the lenses is common. Of 17 of the family members examined by Dr. Bowers, 94% had lens dislocation, 70% had arachnodactyly and 15% aortic disease. Males and females were equally affected and patients usually died in their forties. The males were much less fertile than the females, hence spread of the disease could be stopped if the affected females were stopped from childbearing. Both syndromes appeared to be determined by a single non-sex-linked gene in this family.

Dr. J. B. Boulanger of Montreal made a plea for growing recognition of the importance of psychotherapy and psychoanalysis by the general physician. He described these methods of treatment, together with indications and mechanisms of cure.

Dr. W. H. Feindel of Saskatoon discussed studies on localization of intracranial lesions by use of an automatic brain scanner and radioactive iodinated human serum albumin. This method, which he illustrated by a movie, is still in the state of development, is useful as a screening method, is safe and painless, and could be used on outpatients.

Dr. G. Monckton of Edmonton discussed the biochemical abnormalities found in familial periodic paralysis. In his patient, a man aged 26 with a history of attacks since 16 years of age, studies with radioactive potassium (K^{42}) showed that potassium was not stored in the liver as had been suggested. Then radioactive sodium (Na^{22}) was used, and it became apparent that immediately before and during attacks of paralysis there was a marked sodium retention with a drop in urinary sodium. However, one episode of paralysis occurred at the height of sodium diuresis, suggesting that this was not the only mechanism responsible for paralysis. The patient had no signs of aldosterone disturbance, and reasonable control of the paralysis was obtained by giving a low sodium diet.

General Scientific Meeting

The lectures in medicine and in surgery were given on Saturday afternoon, January 24, by Dr. Murray L. Barr, London, Ont., and Dr. Edouard D. Gagnon of Montreal. Dr. John W. Scott, president of the Royal College of Physicians and Surgeons, was in the chair. Dr. Murray Barr spoke on sex reversal as a cause of male sterility. After outlining the basis of sex chromosome studies, he described Klinefelter's syndrome in which the subject is a male with small testes, fibrosis and hyalinization of the seminiferous tubules, and azoospermia. The patient may have either XX or XY sex chromosomes, but he limited his discussion to those with XX sex chromosomes. The incidence has been assessed by Moore of Winnipeg as 1 in 400 males. The condition is familial, probably in

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part of genetic etiology. Treatment is by testosterone. There is a high incidence of these patients in mental institutions; a study with oral smear technique revealed an incidence of 0.8% of the syndrome in Ontario mental defective institutions.

Dr. Gagnon discussed the recognition and management of traumatic ruptures of the tracheo-bronchial tree. He pointed out that complete and partial tears occur oftener than is realized and that their early diagnosis can lead to the proper management of the case. He confined his remarks to tears associated with closed chest injuries. Such tears were common in the thoracic trachea or bronchi just beyond their bifurcation, because of increased intraluminal pressure. Air escaped into the perivascular sheath and tracked around the bronchi and into other situations.

He divided cases into: (1) tears above the point of pleural reflection, in which the air opened into the mediastinal space and the patient had gross distortion of his surface anatomy by subcutaneous spread of air ("puffball man"). Endoscopy would localize the tear, which could be sutured. Conservative treatment should not be permitted in this type of injury. (2) Tears beyond the reflection of the pleura, which might be associated with a pneumothorax, which might develop early or late. Thoracotomy was not indicated. The case should be carefully observed, since the situation might change at any time. Sometimes a valvular leak would develop, with air dissecting along and into the mediastinum and again producing the picture of the puffball man. Only tracheotomy would be needed; healing was spontaneous. Detection of tears involved a careful history, careful examination, radiography and routine endoscopy in suspicious cases.

Convocation

The above lectures were followed by the presentation of the newly admitted Fellows, and the award of honorary fellowships *in absentia* to Sir Arthur Sims of London, England, and Dr. Donald Balfour of Rochester, Minnesota. Awards were then presented to the medallists in medicine (Dr. J. F. Mustard of Toronto) and surgery (Dr. Peter B. R. Allen of Edmonton), and the meeting closed with the award of diplomas to the two lecturers.

Section of Obstetrics and Gynæcology

The section of obstetrics and gynæcology held two sessions. Friday afternoon was devoted to a panel discussion on perinatal mortality — its definitions and problems, with Dr. F. E. Bryans of Vancouver as moderator. One of the highlights of this session was the description of the Alberta survey of perinatal mortality, and the panel was strengthened by the inclusion of a statistician.

Saturday's session began with a paper by Dr. Y. Yoneda of Edmonton who described a survey of all the cases of abortion (1289) admitted to the University Hospital, Edmonton, over a five-year period. His conclusions from the survey were that (1) in early pregnancy, particularly in a patient with a past history of abortion or a poor obstetrical history, more emphasis on psychotherapy is necessary, with more frequent visits and a better opportunity to assess the emotional and physical status; (2) hormones seemed to be of doubtful value in the management of this problem; (3) most patients after admission to hospital benefit by a dilatation and curettage, because it is difficult by examination of the expelled contents to determine whether abortion is complete or not.

Dr. Margaret Hutton of Edmonton described the perinatal statistics of the University Hospital, Edmonton. She outlined the method of obtaining information, in which obstetricians and pædiatricians collaborated, and attended monthly hospital meetings in association with the pathologist, interns, nursing personnel and other interested or involved staff members. These monthly meetings had led to improvement in charting and had increased the percentage of autopsies. Anæsthesia was now more closely related to the needs of the patient, and the management of babies requiring exchange transfusions was now easier. Perinatal death rate has not changed materially over the years, because of the large number of non-preventable deaths.

Dr. Morrie Gelfand of Montreal described the operation he had performed in a case of imperforate anus with rectovaginal fistula, involving a perineal approach and the bringing of the rectum through external sphincter fibres to a skin dimple in the perineum. The result was good functionally and cosmetically.

Dr. M. G. Tompkins, Jr., of Halifax presented evidence of increased adrenal androgen output in cases of hirsutism with or without amenorrhœa. He noted that prednisone therapy was associated with restoration of the menstrual cycle in 10 out of 14 patients with amenorrhœa or hypomenorrhœa but was not effective in controlling hirsutism. This steroid might be given intermittently to restore the cycle and the fertility.

Dr. D. A. Boyes of Vancouver outlined the objectives of the cytology service in British Columbia and the results obtained. He discussed the organization of the project, the costs entailed, the personnel and training needed, and the expected increase in personnel in the near future.

Dr. J. R. Boyd had collected 14 cases of what he called "occult" invasive carcinoma of the cervix, out of a series of 676 cases of invasive carcinoma. Lesions which measured on the average 1.0 × 0.5 cm. were not clinically perceptible and were found in the tissue removed either by cone biopsy or by excision of the cervix subjected to serial section. One-half of these cases showed lymphatic extension, one-half adjacent preinvasive carcinoma. Nine were treated radiologically and five surgically. Serious complications of treatment were relatively common and three patients are dead while five have a five-year cure.

Dr. H. K. Fidler of Vancouver had investigated 419 cases of intraepithelial carcinoma of the cervix and discovered 26 cases with discrete, scattered microscopic foci of invasion. Diagnosis of this group was poorly defined, and there was a tendency to put too many cases in the group. Evaluation of this type of case was only possible with use of cone biopsy and serial section. Three cases had lymphatic permeation; none of the 26 cases had a recurrence or metastases in the follow-up period, which however was not significant in some cases. The lesion must be distinguished from occult carcinoma in which there were confluent, frankly invasive foci. The lesion with discrete invasive foci seemed to show a pattern of restrained growth which might persist for a relatively long time.

Dr. E. E. Daniel of Vancouver discussed relationships between electrical and contractile activity of uterine muscle in various species during pregnancy and in other conditions. His studies suggested that progesterone diminishes sensitivity of uterine muscle to a stretch stimulus and that in pregnancy progesterone acts locally on muscle overlying the placenta. The progesterone effects are accompanied by characteristic changes in electrolyte metabolism of the uterine muscle with increased permeability to potassium and diminished permeability to chloride and sodium.

Dr. H. G. Wadman of Vancouver had studied cases of fibrinogen depletion occurring in Vancouver hospitals over a three-year period and attempted to determine the actual incidence of fibrinogen depletion in cases of abruptio placentæ. Not all problems of fibrinogen depletion in pregnancy are of course confined to abruptio, death of the fetus and amniotic fluid embolism as is sometimes stated. Some cases in the middle trimester were associated with abortion.

Dr. J. A. Low of Toronto described the four basic steps in the mechanism of fetal oxygenation as (a) oxygenation of maternal blood, (b) placental transfer, (c) oxygenation of fetal blood, (d) tissue utilization. He had investigated the level of function of the mechanism of fetal oxygenation in normal patients at the end of labour and delivery in a series of 750 persons. Results suggested that although they are unstable, the mechanisms of oxygenation of the fetus are unaffected by normal labour and delivery.

DIVISION OF SURGERY

Friday Morning

The case studies of four patients with simple ulcer of the ascending, transverse and sigmoid colon were presented by Dr. M. H. W. Friedman of Edmonton. Diagnosis was made at operation, and local resection performed. Dr. Friedman described a simple ulcer of the colon as an uncommon but interesting lesion of the large bowel, the diagnosis being usually made at operation or autopsy. When situated in the right colon, this ulcer frequently perforated and might simulate appendicitis or other abdominal lesions. When present in the left colon it tended to cause obstruction and might simulate carcinoma.

Dr. F. B. Thomson of Vancouver reported on the follow-up of 222 patients who had a duodenal ulcer combined with evidence of duodenal obstruction. Of those patients who were actually vomiting at their first admission 68% responded to medical treatment and 32% required surgery. However, a further 36% were subsequently readmitted for operation, usually in less than two years. The remainder still have ulcer symptoms. Definite organic duodenal obstruction occurred in 84 cases although in one-quarter of these x-ray examination failed to demonstrate a delay in gastric emptying. If cases are to be diagnosed before extreme starvation has occurred, gastric retention must be measured in all cases of chronic duodenal ulcer soon after hospital admission, and organic duodenal obstruction must be suspected wherever there is significant weight loss. Organic duodenal obstruction, whether partial or complete, is an absolute indication for operation.

Drs. H. S. Dolan, S. C. Skoryna and A. Glay of Montreal discussed six cases of pyloric hypertrophy in adults and related the condition to the anatomy of the pyloric canal, whose circular muscle consists of two sphincteric loops encircling the greater curvature and converging into a muscle torus on the lesser curvature. It would seem that there is a pyloric *canal* mechanism rather than a more limited *sphincter* mechanism.

Dr. J. E. Musgrove of Vancouver had replaced portions of œsophagus and stomach with an intestinal transplant in 12 patients who had undergone either a partial œsophagectomy or gastrectomy. For partial œsophagectomy cases a jejunal transplant was used, while for total gastrectomy a right colon, transverse colon or jejunal transplant was favoured, and for subtotal gastrectomy a transverse colon transplant. After studying the results, the author believed that colonic mucosa should not be anastomosed to a gastric pouch, no matter how small the latter might be, for four out of five patients had developed x-ray evidence of peptic ulcer in a colon transplant.

Dr. Stanley C. Skoryna of Montreal reviewed the surgical methods available for management of chronic ascites. He then described experiments on dogs in which ascites was produced by constriction of the thoracic inferior vena cava either by stainless steel rings or by a plastic (ameroid) enclosed in larger steel rings. He then showed the results obtained with various techniques for relief of the ascites. One series underwent omentopexy and another omentopexy plus splenectomy, while others had a prosthesis resembling a sieve and funnel anchored to the peritoneum and draining either to the exterior or to the space of Retzius.

Dr. C. E. B. Abbott of Edmonton reviewed 25 cases in which operation had been performed for achalasia of the œsophagus; 22 were treated by modified extramucosal œsophago-cardiomyotomy, with various plastic procedures at the junction of stomach and œsophagus. The patients had been followed up for an average of 38 months in the first group and 11 years in the second group. Results suggest that a modified Heller œsophago-cardiomyotomy is the primary treatment of choice in achalasia.

The effects of Thiotepa (triethylene thiophosphoramide) and Nilevar (17-ethyl-19-nortestosterone) on wound healing were discussed by Dr. W. Pisesky of Edmonton, who had studied the bursting pressures of wounds of the abdominal wall in rats. There were three groups, a control group and groups treated by intraperitoneal injection of the two drugs. Thiotepa retarded wound healing while Nilevar counteracted this delay.

Dr. D. L. C. Bingham of Kingston, Ont., gave an account of his experience of surgical treatment of injuries of the common hepatic and common bile ducts in eight cases treated over the last ten years.

Dr. R. M. Janes of Toronto gave a detailed survey of patients with carcinoma of the breast admitted to the public wards of the Toronto General Hospital between 1937 and 1947. (This survey is shortly to be published in the *Canadian Journal of Surgery*.)

Dr. C. M. Couves of Edmonton described experimental and clinical studies of techniques used in local chemotherapy of malignant tumours. He had worked with nitrogen mustard and Thiotepa (triethylene thiophosphoramide) used by organ or extremity perfusion, by lung perfusion, by local application or injection, by intraportal vein injection, by intrahepatic artery in-

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jection, by pulmonary artery injection, intraperitoneally and intrapleurally. Lesions treated included malignant melanoma, sarcoma, gastric carcinoma, hepatoma and bronchogenic carcinoma.

Dr. E. M. Nanson of Saskatoon had investigated the problem of irradiation of parotid salivary gland tumours. Experiments on rats subjected to irradiation of a parotid gland, and a review of the records of the Saskatoon Cancer Clinic for the past 25 years, suggested that irradiation is of definite value in nearly all cases of salivary gland tumour.

Afternoon Session—Orthopædic Surgery

Dr. K. S. Morton of Vancouver had followed up 62 patients with traumatic dislocation of the hip sustained in the period 1936 to 1956. There were six deaths, and four patients had undergone arthroplasty and seven arthrodesis. Of the remaining 45 patients 30 were followed up for two or more years and it was shown that the chief factors governing the outcome of the case were the severity of the injury and the delay in reduction. This delay was mainly due to failure to diagnose the dislocation. Out of 47 known results, seven were excellent, 11 good, six fair, five poor, and 18 failures. The incidence of avascular necrosis is put at 30%.

Dr. D. M. Bruser of Winnipeg reviewed 23 cases of cyst of the lateral meniscus of the knee joint treated by operation. He described his operation for this condition, using the direct lateral approach to the joint which allowed complete and usually intact removal of the cyst with the meniscus, and which was technically more satisfactory than older approaches. The result was very satisfactory, with rapid and usually complete return of function.

Dr. R. J. Cowan of Vancouver had performed 136 tendon sutures on 68 rabbits by various techniques, including end-to-end methods and interlacing methods. The interlacing methods were found better with respect to separation and tensile strength, though the greater cross-sectional diameter was sometimes a disadvantage. These methods were the methods of choice for tendon transplantation. The amount of reaction produced was directly related to the amount of separation of the stumps. This was probably the most important factor in producing good functional results.

Dr. N. P. Merkeley of Winnipeg described the three primary functions of the hand as pinch, hook and grasp, with pinch the most important. He stressed the cardinal importance of never amputating portions of thumb after trauma. Thumb reconstruction might be carried out by local tissue manœuvres, free skin grafting or pedicle flap grafting. Partial loss of a thumb could be made good by phalangization or by use of a tube pedicle with bone grafts. Total loss of the thumb should be made good by transposing the under finger, using a tubed pedicle with bone graft or by metacarpal phalangization.

Dr. F. P. Dewar of Toronto analyzed a series of 145 fractures of the carpal scaphoid recorded by the Workmen's Compensation Board of Ontario in 1954 and 1955. The important result of this analysis was to show that, provided a fracture of the scaphoid was immobilized in plaster, it was very difficult to prevent it from healing satisfactorily. Conservative treatment was the only acceptable one; operation should never be undertaken without previous prolonged immobilization. Even a case in which the fracture had been missed and later put in plaster would end in union.

Dr. P. B. R. Allen of Edmonton, the 1958 medallist in surgery, described his studies of gradual complete occlusion of the hepatic veins. He produced occlusion in dogs by inserting a cannula into the inferior vena cava and pushing it up so as to occlude all the hepatic veins, subsequently suturing it in place and checking by radiography. In four to six weeks ascites and œdema of the hind limbs had appeared; ten to twelve weeks after the operation laparotomy was performed and 3500 to 6500 c.c. of plasma-like fluid (noncoagulable) was removed from the peritoneal cavity. The pressure in the inferior vena cava had increased and in the portal vein greatly increased. The liver was congested but not much fibrosed. There was little evidence of changes in serum electrolytes, but a gradual rise in BSP retention.

Chest Surgery

A study of 115 cases of subphrenic infection seen at the Lahey Clinic in the past few years had been made by Dr. D. P. Boyd of Boston, Mass. Some of these showed intrathoracic complications, which were probably more common nowadays with the chronicity of subphrenic abscess. In some cases the first sign of the latter was profuse expectoration of pus. Cases of bilateral subphrenic infection with bronchial fistula had been seen in which thoracic surgery was not required if the subphrenic abscess was drained. Cases were described in which a postoperative stricture of the bile ducts had led to subphrenic collections of bile by perforation into the pleural cavity with pleural-biliary fistula, while others developed a bronchial-biliary fistula.

Giving the first paper in a forum on open heart surgery, Dr. P. Allen of Vancouver discussed certain problems of intracardiac surgery in the light of experience with 50 cases, in which the bubble-type pump oxygenator had been used. He particularly mentioned the use of a vital stain for outlining the conducting tissue and so preventing often fatal surgical damage to the bundle of His. Dr. J. C. Callaghan of Edmonton reported on the first 100 cases in which a total cardio-pulmonary bypass had been used for operations for congenital and acquired heart disease, with a bubble oxygenator. Dr. A. R. C. Dobell dealt particularly with the changes in acid-base metabolism during extracorporeal circulation.

Saturday Morning

Dr. W. H. Sutherland of Vancouver described a routine screening of patients for hyperparathyroidism. An intensive search for this condition, particularly in persons with recurring renal calculi, had yielded seven cases requiring surgery (not all cases of hyperparathyroidism required surgery, and the author described indications for this). He noted that chemical investigation for hyperparathyroidism was often inadequate, and described a rigid surgical routine with exploration of all possible areas for a parathyroid tumour. Of the seven cases operated on, five were cases of adenoma and two of parathyroid hyperplasia.

Various shunts have been devised to drain cerebrospinal fluid in cases of obstruction, and Dr. J. Stratford of Saskatoon described the ventriculo-caval shunt employed for cases of hydrocephalus, in which the lateral

ventricle was connected to the superior vena cava via the internal jugular vein with a Holter valve, permitting unidirectional flow of fluid. He mentioned the problems encountered in using this shunt; these included blocking of the ventricular catheter due to decrease in size of ventricle, and occlusion of the caval end of the shunt due to clotting and failure of the valve to continue functioning at the relatively low pressure of 50 mm. water at which it was set.

Dr. T. K. Goodhand of Winnipeg had replaced the entire left ureter in nine dogs with a loop of terminal ileum, subsequently removed the other kidney, and killed the dogs after four and a half to twelve months. Results of the experiments showed (1) that an isolated ileal segment is a satisfactory substitute for a ureter, (2) that total replacement of the ureter is probably better than partial replacement because the kidney pelvis and the ileum are of comparable size, though there is a tendency to stricture formation at the junction, (3) that mucus secretion from the ileum simply produces persistent albuminuria, (4) that blood urea nitrogen soon returns to normal, (5) that chloride reabsorption by the ileum is not a problem, and (6) that the isolated ileal segment retains its peristalsis and this tends to prevent reflux and ascending infection.

Dr. T. R. Sarjeant of Vancouver presented the results of extensive surgical treatment of the postphlebitic limb in about 200 cases. Surgery consisted of ligation of the deep vein, stripping of both saphenous veins and fasciotomy, together with excision and skin grafting of ulcers.

Dr. D. R. Wilson of Toronto discussed the surgical aspects of renal artery surgery in hypertension. After describing the history of the Goldblatt syndrome (hypertension produced by partial constriction of renal arteries) the speaker showed that the differential urine volume and sodium excretion test has proved valuable as a screening test for hypertension due to renal artery disease. In a group of 150 cases the test was positive in eight, and subsequent investigation of these showed interference with arterial flow, at least on one side. In one group of younger people, the cause of hypertension was partial obstruction due to a fibrous intimal thickening of the renal artery.

Dr. H. Rocke Robertson of Vancouver discussed the histological results of applying trauma of varying degrees to the external surface of the exposed inferior vena cava of anæsthetized rats. A minimal weight of five grams applied to the surface of the vein for 30 seconds regularly produced changes in the argentophilic intercellular cement substance; application of greater weights showed lesions which were reversible, the speed of reversibility depending on the weight applied.

Dr. T. S. Wilson of Edmonton said that in a large hospital over the past five years cases of chronic breast abscess were half as common as cases of acute abscess. The latter were commonest in the lactating breast of the mother with her first child, and the infecting organism was always *Staph. aureus* insensitive to penicillin in 85% of cases. Treatment was by radial incision, possibly with counterincisions. Novobiocin, erythromycin or chloramphenicol was also given. Chronic breast abscess was most commonly confused with carcinoma; the condition was possibly commoner nowadays because of widespread use of antibiotics. There was little or no sign of inflammation, and the lesion was peripheral or subareolar. Treatment was by excision with or without drainage.

Dr. W. A. Maclean of Edmonton reported three members of a family all of whom had a proven adrenal phæochromocytoma. A positive finding for urinary catecholamine led to pre-sacral oxygen insufflation which outlined the tumour in all cases.

Dr. K. J. MacKinnon of Montreal described the surgical aspects of the recent operation in which renal transplantation in identical twins was carried out. Two operating theatres were used, and a left nephrectomy was performed on the donor twin with preservation of adequate lengths of vessels. In an adjacent operating theatre the recipient area in the right iliac fossa was simultaneously prepared; finally the two renal veins were anastomosed end to side to the external iliac vein and the renal artery was anastomosed end to end to the internal iliac artery. Total period of renal ischæmia was 58 minutes. Within ten minutes a rapid flow of urine began. The ureter was anastomosed to the bladder, a plastic catheter being left in the ureter and the bladder drained by Foley catheter in the dome.

The Annual Dinner

The Annual Dinner of the Royal College of Physicians and Surgeons of Canada was held in the ballroom of the Hotel Vancouver on Saturday evening, January 24, with the president, Dr. John W. Scott, in the chair. Dr. Howard Lewis brought the greetings of the American College of Physicians and Dr. Newell Philpott the greetings of the American College of Surgeons. Dr. H. Rocke Robertson introduced the guest speaker, Mr. Norman Mackenzie, the president of the University of British Columbia, who in an address entitled "The Contemporary Scene" described in detail the work of UNESCO, in the light of his experience as chairman of the Canadian delegation to the Tenth General Conference of that body in Paris last year.

LETTERS TO THE EDITOR

THE DANGEROUS HYPODERMOCLYSIS

To the Editor:

I should like to commend the article in your issue of January 1, 1959, entitled "The Dangerous Hypodermoclysis in Infancy" by S. Israels and K. Wylie of Winnipeg. The authors draw attention to the little recognized but definite danger of hypodermoclysis in small infants.

I would, however, take exception to their advice that therapy to expand the vascular space in severe dehydration with anuria should be undertaken by an electrolyte solution which is half isotonic to that of extracellular fluid. Expansion of the vascular space is most physiologically carried out by the use of 15 to 20 c.c. per kilo of a mixture isotonic with blood. Blood, plasma or, in the less severely affected child, Ringer's lactate solution, are the most suitable for this part of deficit therapy. Once urine flow has been established, hypotonic multi-electrolyte solutions as suggested by the authors would seem to be the logical approach. Although there is a theoretical danger in the face of

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hypernatræmia with this regimen, in actual fact this does not exist. The definition of hypernatræmia is a serum concentration of sodium greater than 150 mEq. per litre; by expanding the vascular space with solution containing 140 mEq. per litre of sodium it is difficult to conceive how this could affect, other than in the proper direction, the level of the vascular sodium.

GERALD H. HOLMAN, M.D.,
Assistant Professor
of Pædiatrics,
University of Saskatchewan.
University Hospital,
Saskatoon, Sask.,
January 15, 1959.

AMERICAN COLLEGE OF SURGEONS IN MONTREAL

To the Editor:

As Co-Chairmen of the Committee on Arrangements for a Sectional Meeting of the American College of Surgeons to be held at The Queen Elizabeth, Montreal, April 6-9, 1959, we are writing to extend a cordial invitation from the Fellows of the College in Montreal to members of your association to attend this meeting.

The program will include separate sessions in anæsthesia, general surgery, gynæcology and obstetrics, ophthalmic surgery, orthopædic surgery, otolaryngology and urology. Extensive programs and hospital demonstrations are scheduled for nurses as well as early morning hospital clinics for general surgeons and surgical specialists. A reception and dinner will be held for visiting surgeons and their wives.

The surgeons in Montreal would be delighted to see good representation from your association in attendance at this meeting.

HARRY S. MORTON, M.D., F.A.C.S., Chairman, and
CHARLES-EDOUARD HEBERT, M.D., F.A.C.S., Co-Chairman, Advisory Committee on Arrangements.
American College of Surgeons,
40 East Erie St.,
Chicago 11, Ill.,
January 13, 1959.

WHO'S FOR KILLARNEY?

To the Editor:

The Irish Medical Association are holding their Annual Meeting at the famous beauty spot Killarney from June 29 to July 3 inclusive. I would be glad if you could kindly insert a notice in your Journal to that effect, as some of your readers may be holidaying in Europe at that time and may wish to attend.

I will forward you, at a later date, a program of the meeting.

NOEL REILLY, M.D.,
Medical Secretary.
The Irish Medical Association,
10 Fitzwilliam Place,
Dublin, Eire,
January 12, 1959.

OBITUARIES

SIR ALDINGTON GEORGE CURPHEY of Claremont, Jamaica, died suddenly in London (England) in December, shortly after he had been knighted by the Queen. He graduated from Queen's University in 1909 and then did postgraduate study in Edinburgh. On his return to Canada he began to practise in Hamilton, Ont., but soon went back to his old home in Jamaica. A few years later he returned to Canada and took over a practice in Toronto for a few months. In the First World War he accompanied a Jamaican regiment to France, and in World War II he was in charge of the Jamaicans in Palestine, where they were highly praised. He held a high position in the Jamaican Government until shortly before the last political change. He was the last white man to hold high office. It was as a reward for his stewardship that he was knighted.

DR. J. V. FOLLETT, 78, died at his home in Calgary, Alta., on December 13. He was born in Newfoundland, and before entering medicine was a school teacher for five years. In 1910 he graduated from the University of Toronto. A year later he started a practice in Exshaw, Alta., and remained there until 1914, when he moved to Calgary. Last October Dr. Follett was made an honorary life member of the Alberta Division of the Canadian Medical Association.

He is survived by two sons and two daughters.

DR. ARTHUR MORRISON HEBB, 86, died on January 13 at his home at Marriotts Cove, near Chester, N.S., after a long illness. He was born in Bridgewater, and attended Dalhousie University, where he obtained his B.A. and M.D. degrees. For 17 years he practised at Chester. In 1919 Dr. Hebb opened an office in Dartmouth. In 1937 he retired to live at Marriotts Cove.

His first wife, Dr. Clara Olding, predeceased him. He is survived by his second wife, a daughter and a son. Another son, Dr. Peter Hebb, predeceased him in 1955.

DR. NEIL MacLEOD, 81, died at his home in Ottawa on December 13 after a long illness. He was born in Roxborough, Ont., and attended the University of Toronto, where he graduated in 1907. Dr. MacLeod was superintendent of the old St. Luke's Hospital in Ottawa until 1909, when he went into private practice. In World War I he served overseas with the Canadian Ambulance Corps, returning to Canada in 1916 because of wounds received in a gas attack. In 1917, while still in the army, Dr. MacLeod was appointed President of the Standing Medical Board in Ottawa and later in Kingston. He resumed his private practice in Ottawa until the outbreak of World War II, when he re-enlisted in the permanent force of the Canadian Army. From 1939-1945 Dr. MacLeod served on numerous medical boards and with the Department of Veterans' Affairs. After the war he returned to his practice, which he continued until his retirement in 1948.

Dr. MacLeod is survived by his widow and a daughter.

BRIGADIER J. L. POTTER, M.D., 81, died in an Ottawa hospital on November 10. A native of Canning,

N.S., he was educated at Dalhousie University. In 1905, while he was working for his F.R.C.S. in London, England, his father died and Dr. Potter returned to Canada. He joined the Army Medical Corps in 1906 and in World War I went overseas with the Canadian Expeditionary Forces. Between the wars he was the District Medical Officer, Canadian Army, at Calgary, Alta., and Victoria, B.C. In 1936 Dr. Potter was made Director General of the Canadian Army Medical Services, an appointment which he held until his retirement in 1940. He was promoted to the rank of brigadier in 1939 after serving 23 years as full colonel.

He is survived by one son.

DR. ANDREW FRASER WEIR, 66, died on January 10 at Hebron, N.S. He was a graduate of Dalhousie Medical School and had practised in Freeport before going to Hebron. Dr. Weir was a veteran of World War I.

He is survived by his widow, and three sons, Dr. Edward Weir of New Westminster, B.C., Dr. Donald Weir of Dartmouth, N.S., and Dr. Andrew Weir, Hebron. Two daughters also survive him.

PROVINCIAL NEWS

ONTARIO

Readers will recall that over two years ago we published the first papers on a drug for treatment of alcoholism. This drug, citrated calcium carbimide, was then thought by the Canadian investigators who developed it to be a better product than disulfiram, which had been on the market a few years. On Wednesday, January 14, at the Alcoholism Research Foundation in Toronto, a press conference for medical editors and writers was called to announce the marketing of this new drug Temposil and to describe its properties.

The Medico-Legal Society of Toronto has recently after prolonged study submitted to the Attorney-General of Ontario a new Act of Legislation to be known as "The Habitué Act" which the Society urges should replace those sections of the Mental Hospitals Act dealing specifically with persons addicted to alcohol or drugs.

The proposed new legislation would enable the police to arrest an alleged habitué in private as well as public places when it appears that he is under the influence of alcohol or drugs and conducting himself in a disorderly manner. Magistrates would have the power to refer persons suspected of being addicts for medical examination. It would no longer be necessary for the family of an habitué to initiate action leading to his restraint in an institution.

Dr. H. S. Dunham of Peterborough, Ont., who has been consulting medical director to Warner-Chilcott Laboratories Limited for the past three years, has been appointed full-time medical director of this division. He has also been elected a vice-president in recognition of the importance of medical research. Dr. Dunham will supervise the clinical research program of Warner-Chilcott and co-ordinate research in Canada with that undertaken by the 38 other divisions of the company throughout the world.

Dr. W. A. Guest has been appointed chief of the Department of Medicine at the Ottawa Civic Hospital.

Kingston Notes

On January 12, 1959, at the regular meeting of the Kingston Academy of Medicine, Dr. Beverley Lynn gave a stimulating talk on the diagnosis of chest conditions, richly illustrated by x-ray films and colour slides with details from his own cases. In introducing him, Dean Ettinger welcomed the academy to the new auditorium of Etherington Hall. This meeting place is a great acquisition to the Medical Faculty at Queen's with its tiers of comfortable seats, controlled lighting, circulating air and facilities for projection of all types of slides and moving pictures. The custom-built podium is so arranged with controls that the speaker at Queen's now has fewer frustrations than at any time in the history of the University. He is even provided with a telephone for direct communication with the projectionist in the booth at the rear of the auditorium. The name of this hall brings back memories of Dr. Frederick Etherington, who was the Dean of the Queen's Medical School from 1929 to 1942. At his death in November 1955, he left more than a million dollars to the Kingston General Hospital and Queen's University, and thus became one of Queen's greatest benefactors.

At the Annual Meeting of the Canadian Association of Radiologists held in Saskatoon in January 1959, Dr. W. A. Jones, Professor of Radiology, Queen's, presented an exhibit of familial fibrous dysplasia of the jaw in three generations of children of the same family. Dr. Jones first reported this condition in 1935. Clinically the condition exhibits as swelling of the upper and lower jaws, producing an unusual appearance to the eyes which are "rolled up toward Heaven" and for this reason he has given the name "Cherubism" to this disease. The most serious complication is loss of all the teeth.

At the January 1959 meeting of the Royal College of Physicians and Surgeons of Canada, Dr. D. L. C. Bingham presented a paper, "Surgical treatment of injuries of common hepatic and common bile duct". The speaker drew attention to certain lessons learned from valuable experience concerning the technical management of such cases and also discussed means of avoiding this type of injury.

Dr. Malcolm Brown is still confined to his home, but we are pleased to report to his many friends that he is progressing well.

R. C. BURR

QUEBEC

Probably the highlight of this month's report from the Quebec Division is the appointment of Dr. H. Rocke Robertson of Vancouver as the chairman and professor of the department of surgery of McGill University and surgeon-in-chief and director of the McGill-Montreal General Hospital surgical clinic at the Montreal General Hospital. Dr. Robertson will take up this appointment on July 1, 1959. A graduate of McGill University in science in 1932 and medicine in 1936, Dr. Robertson has been professor of surgery

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at the University of British Columbia and chief of surgical services at the Vancouver General Hospital and Shaughnessy Hospital since 1946.

On December 1, 1958, Dr. Michael DeBakey, professor of surgery, Baylor University College of Medicine in Houston, Texas, addressed the Montreal Medico-Chirurgical Society on "Surgical considerations of diseases of the aorta and major peripheral arteries". Dr. DeBakey is a leading pioneer on this continent in blood vessel reconstruction and replacement surgery. He dealt principally with indications for intervention and emphasized the technical procedures that are necessary to deal with degenerative, inflammatory, traumatic and congenital lesions of the aorta and major peripheral arteries. He illustrated his talk with many unique and successful replacements which ranged from the ascending aorta to major extremity vessels. Attendance at this lecture was greater than any that we have seen in recent years. Some 250 people were in attendance, and the lecture was followed by a lively and most interesting discussion.

The last Society lecture of the Montreal Medico-Chirurgical Society was given on January 12, 1959, at Queen Mary Veterans Hospital by Dr. Irving S. Wright, professor of clinical medicine, Cornell University Medical College. His subject was "Anticoagulant therapy — progress and problems". Anticoagulant therapy is now well established as an important form of treatment for most thromboembolic conditions. Its use in the treatment of thrombophlebitis, myocardial infarction, thrombosis of the veins without inflammation, embolic phenomena, cardiac irregularities with evidence of embolism, central retinal vein thrombosis and thrombo-embolic conditions involving the cerebral vessels, has been well documented. In his report Dr. Wright summed up evidence in some of the more controversial areas such as the selection of patients, the use of anticoagulants in the face of relative contra-indications, the selection of the anticoagulants of choice for various types of conditions, long-term anticoagulant therapy, the cessation of anticoagulant therapy and other points of issue. As for the previous lecture, the attendance at this session again was outstanding, well over 200 people being present.

Somewhat belatedly, I would like to report a seminar that was held at the Royal Victoria Hospital in Montreal on October 16 and 17, 1958. The theme was "Immunohæmatology and blood banking" and the seminar was arranged by the Ortho Research Foundation and conducted under the direction of Dr. Paul G. Weil of the Transfusion Service of the Royal Victoria Hospital. The speakers were Dr. Philip Levine, director of the division of immunohæmatology; Dr. Robert T. McGee, director of blood procurement, division of serological development; Miss Alice M. Reiss, senior research technician, division of serological development; and Miss Marjory Stroup, supervisor, division of immunohæmatology. Unfortunately, your reporter was unable to attend this seminar because of other commitments but understands that it was most successful and has been of great benefit to all the clinical and technical hæmatology specialists in the Montreal area.

An interesting and unusual ceremony was held at the Montreal Children's Hospital on December 7, 1958. The occasion was the dedication of the new wing of the hospital to Lord Atholstan plus the dedication of the Forbes-Cushing amphitheatre. The ceremony was conducted by Mr. B. M. Hallward, a son-in-law of Lord Atholstan and first vice-president of the hospital.

This function, attended by many prominent lay and professional people and groups of Montreal, replaced an official opening of the hospital. In paying tribute to the three pioneers, Mr. Hallward said, "Dr. Forbes and Dr. Cushing represented the medical world at its best and I like to think of Lord Atholstan as having fulfilled in high degree the social responsibility of those who have an abundance of this world's goods."

The University of Montreal faculty of medicine recently announced new appointments and promotions in the faculty of medicine. Six new professors and four new associate professors were announced. The professors are Dr. Jean-Marie Beauregard — clinical medicine at the General Hospital, Verdun; Dr. Jean Frappier — histology and embryology; Dr. Gustave Gingras — physical medicine; Dr. Marcel Lamoureux—clinical surgery at Maisonneuve Hospital; Dr. Léon Longtin—anæsthesia; and Dr. Louis Poirier—histology and embryology. The new associate professors are Dr. Marcel Ferron — obstetrics; Dr. Réal Gagnon — anatomy; Dr. François Henry — ophthalmology; Dr. Georges Leclerc — dermatology.

La Société Médicale de Montréal has completed a very successful and interesting year. With the beginning of the new year, a new slate of officers has just been elected, as follows: Dr. Jean-Paul Legault, president; Dr. Albert Royer, vice-president; Dr. Gérard Morin, second vice-president; Dr. Georges Leclerc, secretary; Dr. Pierre-A. Turgeon, treasurer; Dr. Gilles Leduc, assistant secretary; and Dr. Louis-Philippe Belisle, councillor. With this outstanding executive we can anticipate an interesting professional year ahead, and your reporter hopes to attend as many of their informative meetings as possible.

Recently a home nursing plan has been worked out between the Montreal General Hospital and the Victorian Order of Nurses. This plan, called a referral system, makes use of the home nursing experience of the Order, and enables patients to leave hospital much sooner and still have the benefit of experienced nursing supervision. Actually the plan had its beginning in 1955, and has now developed into a very effective service. The advantages of this system include the fact that hospital beds can be vacated sooner and, when circumstances are right, patients are better off convalescing in their own homes. A. H. NEUFELD

The list of new directors and executive of the Association of Radiologists of the Province of Quebec is as follows: Executive: Dr. Jean Bouchard, President; Dr. J. S. Dunbar, Vice-President; Dr. O. Raymond, Secretary; Dr. L. I. Vallée, Treasurer. The board of directors also includes: Dr. R. L. DuBerger, Dr. R. G. Fraser, Dr. H. Lapointe, Dr. M. Samson and Dr. I. Sedlezky. The new Secretary is Dr. Odilon Raymond, 5400 Gouin Blvd. West, Montreal 9, Que.

The College of Physicians and Surgeons of the Province of Quebec

At a meeting of the Board of Governors held on December 17, 1958, Dr. Georges Lachaine took up the question of postgraduate training. From the enlightening discussion which followed and during which the deans of the French medical faculties expressed their views, it seems quite evident that the residencies in the hospitals are very satisfactory but that difficulties, mostly financial, exist in so far as basic sciences and magistral teaching are concerned. The Faculties cope with this problem to the best of their ability but feel they could do more if properly aided. There is also the question of refresher courses for practitioners. The Governors listened with sympathy to these statements, and a committee was formed to find ways and means whereby the College can be of assistance.

The draft of the proposed new Medical Act was presented by Mr. Noël Dorion, Q.C., M.P. It is a comprehensive document and is not yet translated into English. Before this is done, a number of alterations have yet to be considered; these will be studied at a special meeting to be held in January or February. One very interesting suggestion would be the carving out of a new district in Montreal to allow another English-speaking representative on the Board. District No. 12 is the most numerous in the province, with almost 900 physicians. About one-third of these are English-speaking and geographically they are fairly well clumped together; it should be easy to form them into a separate group. All the Medical Societies are urged to express their wishes on this question through a written resolution addressed to the Executive Committee of the College; this would certainly carry much weight in the final decision. Perhaps a petition by the physicians concerned could be sent to their Governor, Dr. Lachaine, who is already entirely in favour of this project.

At Dr. Edward Lemieux's instigation, a resolution was adopted requesting the federal and provincial governments to adopt legislation forbidding the sale of x-ray diagnostic equipment to anyone but physicians, dentists, veterinarians and hospitals; the purpose is to protect the public from unwarranted use of ionizing radiations by unqualified people.

Dr. Hervé Gagnon proposed that two councillors be added to the Executive Committee; the purpose is to facilitate its task and enable it to properly meet its responsibilities. After a rather long discussion, the motion was defeated by a vote of 11 to 10. The closeness of the vote clearly shows some uneasiness, and the mere fact of bringing the proposal forward will undoubtedly be beneficial. Dr. Gagnon is to be lauded for his courage in doing so.

Dr. Armand Rioux brought up the very interesting question of legal responsibility involved when a physician issues a premarital certificate of mental and physical health. Unfortunately, the discussion was curtailed by lack of time.

This time element during general meetings is a very awkward drawback. It has been suggested that, instead of four one-day meetings a year, we should have two three-day sessions. This would allow more time for important matters and enable us to receive delegations from various bodies with the attention and courtesy they deserve. Comments from physicians or medical societies on this topic would be appreciated.

The meeting was adjourned to April 8, 1959, with an unfinished agenda.—R. L. DuBerger, Governor of District No. 6 (1054 Prospect St., Sherbrooke, Que.).

NOVA SCOTIA

At a recent meeting, the Board of Directors of the National Heart Foundation of Canada elected Dr. S. J. Shane, assistant professor of medicine, Dalhousie University, to membership-at-large. The National Heart Foundation is a newly formed voluntary health agency which is devoted to research, study, prevention and relief of heart and blood-vessel disease in Canada.

Dr. and Mrs. W. A. Murray and their sons, Kenneth and David, of Oakland Road, Halifax, have left the city for Europe. They will spend the winter in France and Germany, where Dr. Murray will be working with the Royal Canadian Air Force. Later he will go to London for a period of study at the British Post-Graduate School. The Murrays plan to return to Halifax after attending the combined meeting of the British Medical Association and the Canadian Medical Association in Edinburgh in July 1959.

Dr. Howard I. Goldberg of Halifax has returned from attending the annual meeting of the Academy of Dermatology in Chicago.

Mrs. Christine M. MacKenzie, widow of Dr. Kenneth A. MacKenzie, died on December 28, 1958, at the home of her daughter, Mrs. Albert Burditt, in Quebec City. Another daughter, Mrs. William A. Murray, at present in Germany, survives her.

Dr. S. C. Robinson has been appointed to the Department of Gynæcology, Victoria General Hospital. Dr. Robinson was born in Japan. He is a graduate of the University of Toronto and has had extensive postgraduate training in the U.S.A. and in Halifax.

Dr. A. M. Sinclair, who comes from Prince Edward Island, has been appointed to the Department of Orthopædics, Victoria General Hospital. Dr. Sinclair has been trained on this continent and in London and Exeter, England. He is a graduate of Dalhousie, 1952.

At the recent annual meeting of the Amherst Medical Society, Dr. H. A. Myers was elected President, succeeding Dr. R. E. Price. Other officers elected were: Dr. J. A. Langille, Vice-President, and Dr. W. M. Grant, Secretary-Treasurer. Drs. W. R. Morrison, E. G. Kelley, H. E. Christie and G. McK. Saunders were elected as chairmen of committees. Dr. Grant was named medical representative to the Hospital Board of Commissioners and Dr. David Drury representative to the Medical Society of Nova Scotia.

The situation at Yarmouth concerning the construction of a hospital has not been solved. At a meeting held there recently, at which time the local situation was discussed with the Minister of Health, the Hon. R. A. Donahoe, no decision was reached on the suggestion that any hospital built to serve Yarmouth, Argyle and Clare should be staffed, at least partly, by

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the Roman Catholic Sisters. The Town and the Municipality of Yarmouth at first contemplated building a new hospital, but at the same time the Roman Catholic Episcopal Corporation had considered the building of a hospital of their own to serve the same area.

The Hospital Planning Commission visualizes one large regional hospital rather than two smaller units. They further suggested that a single building be built with shared laboratory, x-ray and similar facilities, but with separate accommodation – one section staffed by Sisters, the other by secular staff.

The Hon. Mr. Donahoe promised to give the local hospital problem serious consideration. W. K. HOUSE

PRINCE EDWARD ISLAND

The guest speaker on January 21 in the series of extra-mural lectures sponsored by the Prince Edward Island Medical Society in association with the Dalhousie Post-Graduate Department was Dr. George M. White of Saint John, N.B., who gave a lecture on diagnostic aids in obstetrics and gynæcology.

J. A. MCMILLAN

NEWFOUNDLAND

Newfoundland Medical Board: A recent ballot of the profession in Newfoundland resulted in the election of Drs. G. M. Brownrigg of St. John's and John Burke of Grand Bank to the Newfoundland Medical Board. The Medical Board is the licensing and regulatory body of this province and consists of seven members, four from St. John's and the others from the rest of the province.

New DVA Hospital: The Department of Veterans' Affairs has announced that a Veterans' Pavilion will be erected on the grounds of the General Hospital in St. John's to replace the present DVA ward at the General Hospital.

It is said that architects' sketches are being prepared, but no indication has been given as to when construction will start. The proposed pavilion will give accommodation for "active chronic, and domiciliary care of eligible Newfoundland veterans, together with space for recreational activities". This is one of several additions to the General Hospital envisaged for the next several years. A new wing, with added laboratory, x-ray and operating room facilities, is now nearing completion, and a children's wing and a large residence for nurses are also proposed.

General Hospital Teaching Program: The General Hospital continues to assume increasing responsibility in postgraduate training. The hospital has provided a year of recognized junior rotating internship since 1950, and in 1956 approval was given by the Royal College of Physicians and Surgeons of Canada for one year's training in the specialties of General Surgery, Internal Medicine, Pathology and Bacteriology, and in Diagnostic Radiology.

At the present time each of the clinical departments of the hospital is organizing its activities so as to correlate a first-rate teaching program with a high standard of patient care, and approval is being sought for one year's training in the specialties of Orthopædic Surgery and Pædiatrics. Appointments to the intern and resident staff are expected to be made within the next month.

Personals: In the recent examinations of the Royal College the following local members of the profession were successful:

Fellowship in Obstetrics and Gynæcology—Dr. G. H. Flight.

Certificate in Orthopædic Surgery—Drs. D. G. Landells and A. E. Shapter.

Pædiatrics—Dr. K. Linegar.

Psychiatry—Drs. H. A. Crawford and E. O. Freeman.

Thoracic Surgery—Dr. D. Cant.

Dr. G. M. Brownrigg has been elected a member of the Board of Governors of the American College of Surgeons.

Dr. F. A. Gillespie is leaving the Department of Health in St. John's to begin practice at Tilt Cove. His place will be taken by Dr. G. S. Horner, who has been on the "Lady Anderson".

Dr. C. T. Fitzgerald of Trinity has retired from active practice and gone to live in Nova Scotia. He was eulogized in the Newsletter of the Newfoundland Medical Association by Dr. C. M. MacPherson who spoke of his long and sometimes arduous years of general practice in one of our outports, and of his services to the profession through the Newfoundland Medical Association and the Newfoundland Medical Board.

A. J. NEARY

BOOK REVIEWS

PATHOLOGY FOR THE PHYSICIAN. William Boyd, Professor Emeritus of Pathology, University of Toronto. 900 pp. Illust. 6th ed., revised. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1958. $17.50.

Opinions have varied on the relative merits of the three textbooks which Professor Boyd has written and rewritten through the years, but probably a majority vote would go to his "Pathology of Internal Diseases", of which the sixth edition now appears under a new name. The change of name may be thought to be well deserved, in view of the extensive changes necessitated by a lapse of eight years since the last edition. So many sections, such as the one on congenital heart disease and atheroma, have a completely new look and so many are entirely new, such as the extensive discussion of carcinoid tumours of the intestine, that the author's claim that this is a new book rather than a new edition may in fairness be allowed.

The author notes in his preface that the book is now directed to the graduate rather than the undergraduate, the physician rather than the pathologist. Indeed, some of the sections would be rather tough going for an undergraduate, which seems a pity in view of the pleasure students have derived from earlier editions, but it is no doubt inevitable.

Among other changes in the new book are a contents list at the head of each chapter – rather like the synopses Victorian novelists used to employ to whet the reader's appetite—and a thorough overhaul of the reference lists. New chapters appear on muscle disorders and on the internal environment, and a separate one on joint diseases.

In reading through chapters of the new book, one has the impression that a certain earnestness has invaded the text; the old flashes of wit are there, but the new material has a seriousness which younger readers may not notice but which will not escape older *aficionados* of the Boyd trilogy. But then the book is designed for younger men, and they might feel ill at ease with too much salt of wit on the porridge of modern medicine.

It remains to be said that this is a highly literate and clear account of the subject, and will certainly accomplish the author's purpose of helping candidates to satisfy examiners at specialty examinations.

FORMULARY OF THE MONTREAL GENERAL HOSPITAL.

The Committee of Pharmacy and Therapeutics of the Montreal General Hospital has compiled a very up-to-date and useful formulary which will likely find favour far beyond the hospital premises itself. This formulary is in loose-leaf form, and it is intended to issue each September renewal pages which can be inserted. A great deal of junk has been thrown out of the formulary, including practically all drug combinations unless they have been sanctioned by years of use. The metric system has been used throughout in the hope that it will soon completely replace the imperial system, a hope that all but the most conservative prescribers will echo. Drugs are classified under a series of therapeutic headings, such as analgesics, antineoplastic agents, cardiovascular agents, and respiratory agents. With the classification given, it is easy to find any individual drug very rapidly. In each case, dosage and mode of administration are included, and drugs are listed under their generic names, with well-known commercial names in brackets. This useful pocket-size formulary will no doubt enjoy wide popularity among prescribers. It costs $4.00, including the renewal pages, and is obtainable from Montreal General Hospital, Montreal 25, Que.

THE STRATEGY OF CHEMOTHERAPY. The Eighth Symposium of the Society for General Microbiology. Edited by S. T. Cowan and E. Rowatt. 360 pp. Cambridge University Press; The Macmillan Company of Canada Limited, Toronto, 1958. $6.00.

This book is not for physicians or surgeons but for research workers. It does not deal with strategy in relation to the treatment of human infections by chemotherapeutic substances but explores existing knowledge of various ways by which microorganisms might be attacked without injury to the host, in the hope that a more logical and scientific approach might emerge than the trial-and-error and random screening methods used to reveal the activity of sulfonamides and of many antibiotics.

Ten of the 16 contributions cover such subjects as selective inhibition of cell-wall synthesis, surface active bactericides, membrane penetration and the therapeutic value of chemicals, inhibitors of energy-supplying reactions, designing of antimetabolites, lethal synthesis, selective inhibition of virus multiplication, specific inhibitors of protein synthesis and mechanisms of chemotherapeutic synergy. The opening and introductory contribution by D. D. Woods and R. G. Tucker discusses the general biochemical principles which underlie the interaction of chemical substances with biological systems. The second paper by H. B. Woodruff and L. E. McDaniel of Merck Sharp and Dohme on "The antibiotic approach" deals with the discovery of antibiotics by random screening methods, and it is interesting to learn that of a typical series of 10,000 Actinomycetales strains isolated from soil samples only one was found to produce a new non-toxic and clinically effective antibiotic. The remaining contributions are on metal-binding agents in chemotherapy and the chemotherapy of bacterial infections, fungus diseases, some protozoan infections and amœbiasis.

It is extremely worth while to have noted authorities in various disciplines discuss such fundamental problems. In this symposium, complete with references, the research worker will find many interesting ideas and the accumulated knowledge, incomplete as it is, on the metabolism of host and invading microorganism.

CARDIOVASCULAR COLLAPSE IN THE OPERATING ROOM. Herbert E. Natof and Max S. Sadove, University of Illinois College of Medicine. 197 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1958. $6.00.

The authors have made a critical analysis of causes of cardiovascular collapse in a series of cases in their hospital group. They include a good historical and literature review. Good diagrams portray the incidence of various factors in collapse, and the importance of coronary and pulmonary disease and obstructed airway. It is stressed that a combination of factors is usually the cause and that assessment of general health and risk before operation, correct choice of anæsthesia and proper safeguards before and after are all important. Hypovolæmia, hypoxia, hypotension, anæmia and many other factors are noted. The final chapters on prevention, diagnosis and treatment of cardiovascular collapse are excellent.

MODERN TRENDS IN ANÆSTHESIA. Edited by F. T. Evans and T. C. Gray. 318 pp. Illust. Butterworth & Co. Limited, London and Toronto, 1958. $13.50.

Anæsthesia as it is practised today (1958) in leading teaching centres is discussed in this volume of 22 easily read chapters. Each chapter deals with a specific subject and has been written by a separate author, each a recognized authority in his field. The authors are predominantly British, but some contributions are made from Canada, the United States and Scandinavia.

Among the subjects discussed are the relaxant drugs; new conceptions of consciousness; hypothermia; cardiorespiratory pumps; anoxic states and their treatment; trends in the mode of investigation of anæsthetic problems. A nice balance has been struck between theory and practice. The chapters are compact, with ample references.

This book will be read with interest and profit by all practising anæsthetists, particularly those engaged in teaching. It will also be a source of ready reference to those in all branches of medicine desiring the latest thinking in anæsthesia.

COCCIDIOIDOMYCOSIS. Marshall J. Fiese, Stanford University School of Medicine, Stanford, California. 253 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $10.50.

After the monograph on cryptococcosis by Littman and Zimmerman, we are presented with a further one on coccidioidomycosis, another systemic mycotic infection also known as San Joaquin valley fever. The author has intimate and first-hand knowledge of the disease. The well-illustrated monograph deals with all aspects of coccidioidomycosis. After an introductory paragraph on

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the importance of coccidioidomycosis (245 fatal cases were reported during 1950-54 in California alone), the most interesting and revealing history of the disease is discussed. The mycology of the causative organism, *Coccidioides immitis*, which still presents many unsolved problems, is treated in the third chapter. The subsequent chapters are on the peculiar geographic distribution of the disease and the epidemiology of the airborne infection with its immunological and pathological aspects. The second half of the monograph deals with the clinical aspects of coccidioidomycosis: primary coccidioidomycosis recognized in the U.S.A. 50 years after the first description of the secondary, disseminated form of the disease; benign residual coccidioidal lesions; disseminated coccidioidomycosis or coccidioidal granuloma as first reported from Argentina in 1891 and recognized simultaneously as a separate disease; coccidioidal disease in lower animals which has also been found in Canada; and the treatment of coccidioidomycosis. A comprehensive chronological bibliography lists almost one thousand references to papers published up to 1957.

Since a few cases of this systemic mycotic infection have already been recognized in Canada, this detailed and revealing monograph can be highly recommended.

CONGENITAL ANOMALIES OF THE HAND AND THEIR SURGICAL TREATMENT. Arthur Joseph Barsky, Mt. Sinai Hospital, New York, N.Y. 165 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $6.25.

A complete and exhaustive study of a large variety of congenital hand anomalies and their surgical treatment is presented in this monograph. The material is drawn from the author's own experiences with 165 personal cases, as well as his survey of relevant medical literature.

In a concisely written and well organized book, the author deals first with the incidence and etiology of these conditions, posing certain pertinent questions and attempting to answer them. He emphasizes that genetic factors are the principal causes of most anomalies. He then presents a large series of interesting cases describing the clinical features and incidence, as well as the detailed surgical treatment in step-by-step fashion.

Abundantly sprinkled with photographs and diagrams, the book has merit as a reference source, but its usefulness is particularly restricted to those actively concerned with the management of the rarer hand problems.

APPLIED PHYSIOLOGY OF THE EYE. H. Willoughby Lyle. 341 pp. Illust. Baillière, Tindall and Cox, London; The Macmillan Company of Canada Limited, Toronto, 1958. $7.65.

This is a well-written review of both basic anatomy and physiology with regard to their clinical application in ophthalmology. The book contains many facts related to general medicine, surgery, pathology and physiology which concern the function of vision. There is a list giving the Greek derivations of certain words relating to ophthalmology, and a list of names associated with certain ophthalmic diseases and syndromes.

Its main purpose is to present a general brief review for graduate students preparing for higher examinations rather than a simple introduction to ophthalmology from an undergraduate teaching level. Since the book is only 300 pages long, no single subject is discussed in very great detail.

BRAIN TUMORS: Their Biology and Pathology. K. J. Zülch, University of Cologne; translated by Alan B. Rothballer, Albert Einstein College of Medicine, New York, and Jerzy Olszewski, University of Saskatchewan, Saskatoon. 308 pp. Illust. American edition based on the 2nd German edition. Springer Publishing Company, Inc., New York, 1957. $9.50.

There is no generally acceptable classification of brain tumours. A fairly wide disagreement exists over the question of tumour cell origin, partly because a true understanding must be linked with a knowledge of causation, and that, of course, is completely lacking. There is much closer agreement (because the facts are readily accessible) on the manner in which tumours of different histological appearance are likely to behave clinically. Thus over the years a fairly close correlation has been established between histological and clinical degrees of malignancy. The result is that the most acceptable classifications on the whole are those that have proved to be most useful clinically. They are not always those that clarify our understanding of the more fundamental aspects on oncogenesis. Present cellular research—biochemical, genetic and biological—may soon make orthodox cancer classifications and language obsolete (for example, "anaplasia" or "dedifferentiation", terms introduced to convey the meanings of certain hypotheses). Professor Zülch touches on some of the directions in which cancer research is proceeding, although this is not the strongest part of his book. Its value lies in its thorough and comprehensive orthodoxy; there is a skilful presentation of controversial issues which makes for excellent reading. It is based on a large volume (4000 cases) of material personally studied by the author. There is an extensive bibliography. The occasional quaintness of style, so hard to avoid in a translation, does not distract the attention of the reader. Rothballer and Olszewski are to be congratulated for having undertaken so successfully the thankless task of translation.

THE MAMMALIAN CEREBRAL CORTEX. B. Delisle Burns, McGill University, Montreal. 119 pp. Illust. Edward Arnold Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1958. $3.60.

This monograph of a hundred pages deals with a complicated problem of neurophysiology. It presents up-to-date information on the intimate functioning of the cerebral cortex. Modern electrophysiological techniques are not difficult to apply if an electronic expert is available to maintain your equipment. The interpretation of the results, however, leaves much room for discussion and argument. Professor Burns has presented his own observations with enough basic electrophysiology to make the results comprehensible. The reader not acquainted with this type of work may be discouraged by the first half of the book, but the second half presents a somewhat broader, more philosophical approach. This is not an armchair type of philosophy, but is heavily interlarded with the specific observations of many authors.

The book is clearly and concisely written and there is no confusion about the author's meaning. The illustrations are adequate and to the point, well done and easily understood. The bibliography is extensive and the index adequate.

This monograph will be appreciated by all those interested in cerebral function. It is, however, a specialized field and the material will not appeal to the majority of medical men.

NO MORE WAR. Linus Pauling, Pasadena, California. 254 pp. Illust. Dodd, Mead & Company Limited, New York and Toronto, 1958. $4.00.

The issues behind the continuation or abolition of nuclear testing by the so-called Great Powers have by now been so obscured by the forces of emotion and vested interest that it is difficult for the man in the street to know just what is at stake. Professor Pauling attempts to explain to the intelligent layman what are the basic chemical and physical principles behind nuclear warfare, and what the continued testing of nuclear weapons, and their use in nuclear warfare, may imply. He has of course been reviled and denounced for his views, whose importance is no doubt in direct relationship to the amount of denunciation. One is uncomfortably reminded of the attitude in the thirties to Charles de Gaulle when he told France how worthless her Maginot Line was.

It is almost too much to hope that any of the politicians will pay any attention to Professor Pauling's book or to his suggestion for a long overdue organization for research on peace. It is, however, almost a duty for intelligent persons to read this book and learn what a large number of the world's scientists are thinking about the future of the world we live in.

COFFEE AND CAFFEINE. Rolf Ulrich. Translated by Janet Ellingham. 52 pp. John Wright & Sons Ltd., Bristol; The Macmillan Company of Canada Limited, Toronto, 1958. $1.30.

In this little monograph, Dr. Ulrich reviews the literature on coffee, with particular reference to those articles appearing in the German language. Dr. Ulrich discusses the effects of caffeine on the human body, noting its cardiovascular and renal effects, its effects on nerve and muscle, and its metabolic effect. He then devotes a section to the subject of coffee in medical practice, giving a list of diseases in which coffee should be forbidden; this list includes certain heart diseases, hypertension, dermatitis, certain cases of pulmonary tuberculosis, hyperthyroidism, gastric and duodenal ulcers, chronic cystitis and glaucoma. He has very strong views on the abuse of coffee in sport, and exposes the fallacies of its use as an antagonist to alcohol consumption for car drivers. Among the many curious pieces of information in this book, surely the most curious is the fact that caffeine is toxic to the gonads of black rabbits.

KLINISCHE FUNKTIONSDIAGNOSTIK (Clinical Diagnosis of Function). H. Kuchmeister, Hamburg. 445 pp. Illust. 2nd ed. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1958. $11.80.

A short review of the first edition of this book was published here about one year ago. The necessity for a second edition within such a short period of time proves the wide use the book found.

The text of the new edition contains 30 more pages, most of which are devoted to the chapter on diseases of the blood. Tests using radioactive isotopes are described, making possible, for example, determination of the life span of erythrocytes with radioactive chromium or exact determination of absorption and excretion of radioactive vitamin B_{12}.

The bibliography has been extended and brought up to date, reviewing the world literature up to 1957. The number of illustrations has also been increased.

THE PRACTICE OF INFECTIOUS DISEASES. L. Weinstein, Boston. 501 pp. McGraw-Hill Company of Canada Limited, Toronto, 1958. $8.93.

All conditions caused by microbic organisms—bacterial, viral, protozoal, mycotic, etc.—are described in this volume, which deals with infections in the widest sense. The writing is clear and the presentation methodical. The work is laid out and the conditions are described on an anatomical basis; the author starts with the mouth and proceeds via the chest to the abdominal and pelvic organs; the central nervous system, muscles and skin are then dealt with in that order. A final chapter is given over to discussion of fever of obscure origin. This arrangement, while no doubt appealing to the student preparing for examination, nevertheless entails repetition. For instance, tuberculosis is discussed in the chapter on infections of the upper respiratory tract and again in the chapter on lower respiratory tract diseases, again in diseases of peritoneum and intestinal tract and so on. This arrangement will not appeal to the general practitioner to whom the work is addressed, for if he wishes to refresh his memory on the various manifestations of tuberculosis he will not have the time to read through four or five chapters to do so. Again, the chapter on the exanthemata is relatively short, and one feels that the chapter on fever of obscure origin could have been expanded and given more prominence, since it is when confronted with this condition that the general practitioner would turn to such a work for advice and guidance. One last point—when advising dosage of some of the antibiotics, the dosage is given as so many mg. per kilo body weight. For the general practitioner, this is not very helpful and calculation in pounds would have been more useful.

In conclusion, one might say that this book will prove useful to the examinee and to the physician who wishes a shortened refresher course.

SONDERAUSSCHUSS RADIOKTIVITAET BUNDESREPUBLIK DEUTSCHLAND. Erster Bericht. First Report of the Special Committee on Radioactivity, West Germany. 68 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1958. $1.10.

A special committee on radioactivity has been sitting in the West German Republic, and has now published its first report. This committee considered that its first and most urgent matter was to determine so far as possible the contamination by radioactive fallout in Western Germany, with special reference to air, water, soil and foodstuffs. It made contact with all the bodies in West Germany concerned with measurement of radioactivity in these areas. Evaluation of data obtained from them all shows that the results correspond closely to those observed in other countries. It was clearly shown that in recent years contamination of air, water, soil and foodstuffs has risen, corresponding to nuclear weapon testing.

The minimal values for specific radioactivity of the atmosphere close to the earth increased between 1955 and 1957 by a factor of five times. The median specific strontium-90 activity of milk increased between 1955 and 1957 by the factor of three. The committee considers that the supervisory measures for contamination of air and soil are adequate; it suggests a step-up in determination of contamination of foodstuffs. There is no actual danger at present, but it also suggests that the situation requires close watching.

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PROCEEDINGS OF THE NINTH ANNUAL CONFERENCE ON THE NEPHROTIC SYNDROME. Held at the National Institutes of Health, Bethesda, Maryland, October 24-26, 1957. Edited by J. Metcoff. 248 pp. Illust. Sponsored by the National Nephrosis Foundation, New York, 1958.

The *Proceedings of the Ninth Annual Conference on the Nephrotic Syndrome* contains some sections of great interest. Among the most valuable ones are those by Germuth on experimental anaphylactic glomerulonephritis and human nephritis, that of Gordon on unesterified fatty-acid metabolism, of Davis on aldosterone and sodium retention in dogs with experimental ascites, and of Gribetz on tissue electrolytes, nephrosis, and DOCA administration. The contribution of Riley on steroid therapy of the nephrotic syndrome is also of interest.

It is very commendable that these conferences, held for the past nine years, should be "informal with emphasis on discussion", but this should not prevent the editor from doing a little formal editing. No word is said about the sponsors of the conference and there is no list of participants and of their origins. Too often, the discussion is rambling and repetitious, but the most annoying feature is the repeated referring of participants to one another as Jack, Jim, Don, Con, Walter and so on.

The introduction on Page 1 is really of no interest to the readers: "Dr. Howard Goodman (National Heart Institute): Perhaps the weather has held up Dr. Heymann. (Dr. Heymann entered the meeting.) It could not be a better time, Dr. Heymann. Will you come in and make yourself comfortable, then let me ask you to chair this afternoon's meeting. Dr. Heymann! (Dr. Walter Heymann, Western Reserve University School of Medicine, Department of Pediatrics, assumed the chair.) Chairman Heymann: I usually am on time; but I thought that one-thirty p.m. was scheduled so that we would all be here by two o'clock. (Laughter.) Thus I thought I would be fifteen minutes early. I apologize for being late just the same and quote as an excuse that we drove from Cleveland."

An example of poor discussion is found on page 195: *"The French literature suggested* that there was something called a deposition of 'dry' salt some place in the body during accumulating œdema." It is quite a broad statement to assume that Blum and Van Coularert are "the French literature" and it is a statement one would like to check carefully for accuracy.

It is to be hoped that editors of future proceedings of important conferences such as these will follow the principles laid down by such groups as the Laurentian Hormone Conference and the Ciba Foundation.

DAS KLAPP'SCHE KRIECHVERFAHREN (The Klapp System of Creeping Exercises). Bernhard Klapp. 79 pp. Illust. 3rd ed. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1958. $3.20.

Klapp was a well-known German surgeon who was born in 1873 and died in 1949. His particular interest in life was the correction of deformities of the spine, such as scoliosis, and over a long period he developed a system of exercises carried out by his pupils on hands and knees (the so-called Klapp system of creeping exercises). The present volume describes in great detail and with a large number of illustrations the system of exercises associated with his name.

ABSTRACTS *from current literature*

MEDICINE

Hypoxia of Abnormal Physiologic Origin as the Final Common Pathway in Gastroduodenal Ulcer Genesis.

E. D. PALMER AND J. L. SHERMAN: *A.M.A. Arch. Int. Med.*, 101: 1106, 1958.

A comprehensive review of the anatomy, physiology, pharmacology and pathology of the arteriovenous shunt system in the gastroduodenum serves as the basis for a discussion of the genesis of peptic ulcer. Observation of the great incidence of ulcer, and the propensity of the lesion to repeat over and over the cycle of breakdown and healing, convinced the authors that the final common pathway of peptic ulcer is a physiological process gone wrong. Mucosa may be rendered hypoxic under conditions of capillary congestion or plethora, as well as under those of ischæmia. Both extremes are able to depress mucosal vitality to the point of necrosis, but the authors point to the observation of mucosal engorgement associated with erosions as favouring the condition of plethora as the usual explanation for local hypoxia, which is the first step in crater formation. The authors admit that this theory of ulcer genesis does not explain the localized nature of ulcers, their tendency to recur in the same spot, the development of anastomotic ulcers, and other features of ulcer. It does, however, explain the effectiveness of vagotomy because the latter influences vascular control, which is an important function of the vagus rather than the secretory one. The authors believe that gastrectomy too is at least partly effective because of the vagotomy which it produces.

W. GROBIN

Encephalopathy in Pulmonary Disease.

H. BACCHUS: *A.M.A. Arch. Int. Med.*, 102: 194, 1958.

In two cases of advanced pulmonary disease, presenting symptoms were those of encephalopathy. In the first patient the clinical diagnosis was of cerebral tumour but at autopsy no other abnormality of the brain was found beyond marked congestion of the cerebral vessels. In both patients marked confusion, disorientation, ataxia, severe headaches and "thick speech" were much more striking than the underlying pulmonary disease. Polycythæmia and ruddy cyanosis were present in both, and the second patient had cor pulmonale with right ventricular failure. Her encephalopathy developed in hospital while she was on decongestive treatment, and the spinal fluid pressure at that time was found to be 500 mm. of water. On symptomatic treatment with intravenous fluids (dextrose 10% in water) she improved within 10 hours.

The author discusses the mechanism by which this encephalopathy develops and points to the low protein level in the spinal fluid in both cases. This apparently had also been reported by other observers. Because of the importance of this syndrome and the possibility of confusing it with cerebrovascular disease, brain tumour and hypoglycæmia, the author stresses the following features of this syndrome: (a) underlying lung disease, (b) evidence of secondary polycythæmia, (c) clinical pattern of headaches, stupor, or coma, associated with areflexia or with focal neurological signs, (d) increased cerebrospinal fluid pressure associated with papillœdema and retinal vein engorgement, and (e) low cerebrospinal fluid proteins. W. GROBIN

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(Continued from page 322)

Experimental Coronary Artery Occlusion: Ventricular Fibrillation and Survival as Affected by Selected Drugs and Ionic Alterations.

W. T. WILLIAMS *et al.*: *Dis. Chest*, 34: 317, 1958.

The effect of selected drugs and various inorganic ions on ventricular fibrillation and mortality after experimental coronary artery occlusion was investigated. A control figure of 80% mortality and 30% early fibrillation was obtained, after ligation of the left anterior descending coronary artery immediately at its origin. When coronary occlusion was delayed for 20 days after pericardiotomy in three animals, none died and two of the three animals showed no change in the electrocardiograms. This may have been due to establishment of adequate collateral circulation.

Mortality rates varying between 60% and 100% with similar fibrillation rates resulted from induction of acidosis, alkalosis, hyperkalæmia and hypercalcæmia, and from intravenous infusion of sodium chloride, procaine, papaverine and quinidine.

It would appear from this study that if potassium is the excitatory agent for ventricular fibrillation, myocardial metabolism of potassium in myocardial ischæmia is unaffected by blood pH with respect to decreasing early fibrillation. None of the drugs or ions employed in this study showed reduced mortality or ventricular fibrillation after coronary artery occlusion. This is considered to be the crucial conclusion from this study.

S. J. SHANE

Genetic Aspects of Cardiovascular Diseases.

V. A. MCKUSICK: *Ann Int. Med.*, 49: 556, 1958.

It appears that heredity plays a certain part in all the four principal types of cardiovascular disease: atherosclerosis, hypertension, rheumatic fever and congenital malformations.

The bulk of the present article is concerned with the discussion of cardiovascular aspects of Marfan's syndrome. The multiple components of this syndrome are presented. The ascending aorta is primarily implicated, by diffuse dilatation or by dissecting aneurysms or by both. However, in rare cases, it appears that the *abdominal* aorta is primarily implicated. Marfan's syndrome appears to depend upon a single genetic mutant, which behaves like an autosomal dominant. The nature of the basic defect of the connective tissue is not thoroughly understood. However, the elastic fibre — or an element intimately associated with it — comes under suspicion.

S. J. SHANE

Acute Hepatic Congestion and Elevated Serum Glutamic Oxaloacetic Transaminase Titres.

L. H. SHIELDS AND R. E. SHANNON: *Am. J. M. Sc.*, 236: 438, 1958.

An analysis of serum glutamic oxaloacetic transaminase (SGOT) titres greater than 400 units led to the conclusion that acute hepatic congestion can cause such elevations. When the congestion is severe, high titres above 500 units can result; where the congestion is severe enough to cause hepatic necrosis, titres up to 3000 units may occur. The importance of the hepatic congestion factor in SGOT titres is emphasized by the significant difference of the average titre in uncomplicated myocardial infarction (482) and the average titre in all cases of acute hepatic congestion (1042), irrespective of etiology. Not infrequently, acute myocardial infarction may be associated with SGOT titres greater than 400 units. In patients with myocardial infarction, titres above 650 units should lead one to suspect that functional hepatocellular injury due to congestion is present as well.

Whereas high transaminase levels in myocardial infarction not accompanied by liver congestion have no short-term prognostic value, high titres in myocardial infarction associated with acute hepatic congestion suggest a poor prognosis for the patient, and shock is more likely to complicate the clinical course.

S. J. SHANE

SURGERY

Idiopathic Retroperitoneal Fibrosis.

E. HACKETT: *Brit. J. Surg.*, 46: 3, 1958.

In the past 10 years there have been reports of about 20 cases of ureteral obstruction by an unusual retroperitoneal fibrotic lesion. This fibrosis may involve the aorta and inferior vena cava and is therefore not only of urological interest. Further, it is suspected that the lesion is much more common than would appear, for several cases have been found in one centre in a short period.

There is a dense flattened plaque of fibrous tissue anterior to the vertebral bodies and the fascia over the iliopsoas muscles which may either cross the midline and surround the great vessels, or remain unilateral. It does not extend into the mesentery or above the crura of the diaphragm or below the bifurcation of the iliac arteries. It has reached 2 cm. in thickness. It is composed of fibroblasts and collagen-like scar or keloid. Signs and symptoms vary according to whether it reduces the pliability of the spine, or lessens blood supply to the lower extremities, constricts venous return or causes hydronephrosis. Thus backache, intermittent claudication, swelling of the legs, oliguria or hydronephrosis may result.

Two more cases are reported from Dublin.

Treatment is surgical and it may be life-saving. Ureters may be successfully freed and transplanted into an intraperitoneal position to avoid recurrence. It is considered that in most cases the fibrosis is the result of organization of a hæmatoma or a fibrinous effusion.

BURNS PLEWES

The Effective Level of Lumbar Sympathectomy.

W. C. RANDALL *et al.*: *Ann. Surg.*, 148: 51, 1958.

Preliminary to resecting the lumbar sympathetic trunk, direct electrical stimulation at various levels was used to determine sweating responses over the lower extremity as demonstrated by the iodine-starch-paper technique.

It was found that the levels of the trunk that control sympathetic functions of the skin vary widely from patient to patient and even from one side to the other of the same patient. Preganglionic sudomotor fibres to the lumbar trunk may enter at L1-L3 in some, L2-L3 in some, and L3-L5 in others, and there is no way of predicting which two or three ganglia should be resected to interrupt the pathway in a given patient.

More frequently satisfactory results will follow lumbar sympathectomy for arterial disease of the lower extremities if an extensive operation (L2-L5 or even L1-L5) is done.

BURNS PLEWES

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Parotidectomy for Chronic or Recurrent Sialadenitis.

H. C. KEENAN, O. H. BEAHRS AND K. D. DEVINE: *Surg. Gynec. & Obst.*, 106: 573, 1958.

Chronic sialadenitis presents as a recurrent or persistent painful swelling in one or both parotid glands. The condition varies greatly in frequency, duration and severity of the episodes. Some patients have an occasional mild bout of pain and swelling, while others have frequently recurring or constant distress over a period of years.

Calculi may be associated with the condition, either as a single stone in Stenson's duct or as multiple small calculi scattered throughout the parenchyma of the gland. The former may occasionally produce the clinical picture of chronic recurrent parotitis; the latter is usually the result of severe, long-standing disease.

The etiology of the condition in most cases is obscure. It is not surprising, therefore, that the numerous methods of conservative treatment give inconsistent and questionable results. Such methods have included roentgen therapy, dilatation of Stenson's duct; removal of septic foci in the oropharynx; agents to decrease the viscosity of salivary excretions such as pilocarpine and potassium iodide; massage; vaccines and antibiotics. No single method has been demonstrated to be superior to the others.

The authors advise subtotal or total parotidectomy for the more severe cases. The criteria for the selection of patients for surgical treatment are not clear-cut, but are based primarily on the severity and persistence of symptoms. The cases selected were considered to have glands irreversibly damaged by the disease. Sialography was not utilized as an aid in the selection of patients for operation.

Superficial parotidectomy, with identification and preservation of the facial nerve (as described by Janes), was used in preference to total parotidectomy. The subtotal removal of the gland was considered to be simpler technically, and produced equally good results. Total parotidectomy is advised if marked cystic dilatation involves the deeper portion of the gland.

The five patients so treated, one with bilateral disease, had excellent cosmetic results and were relieved of their symptoms. JOHN PALMER

Surgical Considerations of Occlusive Disease of the Abdominal Aorta and Iliac and Femoral Arteries.

M. E. DEBAKEY, E. S. CRAWFORD, D. A. COOLEY AND G. C. MORRIS, JR.: *Ann. Surg.*, 148: 306, 1958.

The obstructing lesion in chronic arteriosclerotic occlusive disease of the lower extremities is usually well localized and segmental, with a relatively normal patent lumen above and below. There are two major groups of occlusions: aorto-iliac and femoral. Associated disease of the peripheral arterial bed was present in 18% of these cases. Effective therapy is permitted more often when arteriographic studies are done.

Three types of surgical procedure were employed: thromboendarterectomy, excision with graft replacement, and the bypass graft; each method has its indications. Lumbar sympathectomy is considered a desirable supplementary procedure in cases in which there is associated peripheral narrowing or occlusion in the smaller distal arterial bed.

The results have been successful in 95% of cases. The operative mortality of 2.7% was most often due to associated cardiac and renal disease. Recurrent occlusion was encountered in only eight patients.

When the occlusive lesion is quite discrete and well localized, thrombo-endarterectomy may be best. When the occlusion is long and extends into the femoral artery, a bypass graft is the procedure of choice.

Long-term results of these operations were considered satisfactory. Especially noted is the success of a second operation for recurrent occlusion in 20 out of the 27 patients in whom it was attempted.

BURNS PLEWES

THERAPEUTICS

Evaluation of Chemotherapy in Pulmonary Tuberculosis. Part I: High Doses of Isoniazid with PAS and Pyridoxine.

S. J. BERTE, H. J. DEWLETT AND H. W. SCHMIDT: *Am. Rev. Tuberc.*, 78: 773, 1958.

This paper suggests that the use of high doses of isoniazid with PAS provides superior results in all phases of clinical evaluation.

Of 84 patients 75% had adequate free-serum isoniazid concentrations. One-fourth of the patients had detectable concentrations between 0.3 and 0.8 μg. of free isoniazid per ml. six hours after one-third of the total daily dose of isoniazid and PAS had been given. No correlation could be made between free-serum isoniazid concentrations and reversal of infectiousness, because in more than 97% of all patients the sputum was negative for tubercle bacilli on culture at six months.

The occurrence of peripheral neuropathy is not to be feared when 100 mg. of pyridoxine is administered once daily. Perhaps a lower dose of pyridoxine might be just as effective. Antagonism of biologically active isoniazid by pyridoxine was not detectable in the clinical results. The incidence of gastro-intestinal intolerance due to PAS was less than 5%. This is attributed to the use of a freshly manufactured preparation delivered to patients within two months of its manufacture. S. J. SHANE

Evaluation of Chemotherapy in Pulmonary Tuberculosis. Part II: Daily Streptomycin Plus High Doses of Isoniazid with PAS and Pyridoxine.

S. J. BERTE, H. J. DEWLETT AND H. W. SCHMIDT: *Am. Rev. Tuberc.*, 78: 779, 1958.

There appears to be no advantage to be gained by adding daily streptomycin for 90 days to drug regimens containing high doses of isoniazid and PAS. It is of interest, however, to note that 20.1% more cavities less than 2 cm., and more cavities greater than 4 cm. in size, closed in six months when daily streptomycin was added to high doses of isoniazid and PAS.

Although reversal of infectiousness and roentgenographic improvement are not enhanced by daily streptomycin, it is of interest to speculate whether or not daily streptomycin with high doses of isoniazid and PAS will produce better cavity closure than will high doses of isoniazid and PAS without streptomycin. A much larger study will be needed to answer this question.

A general comparison with other studies utilizing intermittent streptomycin and lower doses of isoniazid and PAS was made. There are indications that the

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substitution of daily streptomycin and high doses of isoniazid in such a triple-drug regimen can enhance cavity closures and roentgenographic improvement.

S. J. SHANE

Toleration, Absorption, and Clinical Efficacy of Para-Aminosalicylic Acid Preparations in Tuberculosis.

S. S. COHEN, W. Y. YUE AND S. H. TSAI: *Am. Rev. Tuberc.*, 78: 899, 1958.

In this study 300 patients with minimal, moderately advanced or far advanced pulmonary tuberculosis were divided at random into four groups, each group receiving one of the following preparations: a PAS-ion exchange resin complex, sodium-PAS, potassium-PAS, or calcium-PAS. Isoniazid and other antimicrobial agents were administered in conjunction with these preparations.

Comparison of the gastro-intestinal toleration of these preparations administered daily for two to 12 months indicated that a *PAS-resin complex* was the best tolerated preparation, causing fewer and less severe symptoms than the others. No correlation existed between the absorption and the para-aminosalicylate content of the preparations, since the potassium salt, which was most extensively absorbed, supplied the least amount of PAS per dose.

In 155 selected patients observed for four to 12 months, all four preparations were almost uniformly effective in preventing or postponing development of resistance to isoniazid or other antimicrobial agents employed. No significant differences were observed between preparations with respect to numbers of patients showing roentgenographic improvement.

S. J. SHANE

DERMATOLOGY

Cutaneous Reactions due to Sulfamethoxypyridazine.

D. G. LINDSAY *et al.*: *A.M.A. Arch. Dermat.*, 78: 299, 1958.

Sulfamethoxypyridazine is an antibacterial agent used in the treatment of urinary tract infections. Of 85 patients receiving this drug, 13 developed an erythematous maculo-papular dermatitis. One patient gave a history of previous reaction to sulfonamides, but five of those reacting to sulfamethoxypyridazine had previously taken sulfonamides with no side effects. One drug eruption started 42 days after the onset of taking the drug; all the others started within 15 days. One patient was hospitalized for two months as a result of the dermatitis; all the others showed rapid disappearance of the rash after the drug was stopped. There was some indication that, with daily doses of 0.5 g. or less, a lower incidence of reactions may be expected.

ROBERT JACKSON

Philodendron as a Cause of Contact Dermatitis.

S. AYRES, JR. AND S. AYRES, III: *A.M.A. Arch. Dermat.*, 78: 330, 1958.

The authors present twelve cases of contact dermatitis from several species of philodendron, especially *Philodendron cordatum*. All had positive patch tests. Linear erythemato-vesicular lesions were present in many; these made distinction difficult between philodendron dermatitis and poison ivy (or poison oak) dermatitis.

ROBERT JACKSON

MEDICAL FILMS

CONTINUING the listing of available films on medical and related subjects, we list below additional films. The films are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 142 Sparks Street, Ottawa, Ontario. The evaluations have been prepared by Canadian specialists in the subjects of the films, under the Medical Committee of the Scientific Division of the Canadian Film Institute, which is headed by Dr. G. H. Ettinger.

Cardiac Arrest—1957; Sound; colour; 17 minutes.

Produced by Verity Films (Oswald Skilbeck, M.A.) for Imperial Chemical Industries Limited. Technical advisers: John Beard, M.D., F.F.A., The Post-Graduate Medical School of London.

Description.—An instructional-training film setting forth a technique for dealing with cardiac arrest by opening the chest wall and massage. Causes of cardiac arrest are discussed and massage is shown on a model of the heart. A sudden, naturally occurring arrest is shown in an elderly person and the circumstances under which cardiac massage would result in a successful outcome are discussed. The various steps of the technique are outlined in detail, in the case of a young subject going into arrest following induction of anæsthesia. Emphasis is put on speedy institution of a pre-determined sequence of actions designed to produce a circulation within three minutes. The anæsthetist is seen performing the thoracotomy and instituting massage until surgical assistance arrives. The place of drugs is discussed. A heart in fibrillation is seen and restoration of a normal rhythm observed.

Appraisal (1958).—A well-produced and logically developed presentation of the current thinking on both causes for and treatment of cardiac arrest. Recommended for general practitioners doing surgery, for medical students in the clinical years, for nurses and for anæsthetists. It might have been mentioned that it is advisable to have the operating surgeon in the immediate vicinity when anæsthesia is induced. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($3.00). For purchase apply to Publicity Department, Imperial Chemical (Pharmaceuticals) Limited, Fulshaw Hall, Wilmslow, Cheshire, England.

PHYSIOLOGY

How the Eye Functions—1940; Sound; B & W; 12 minutes.

Produced by McCrory Studios, New York, N.Y.

Description.—An instructional film, demonstrating the elementary physiology of the eye. The film employs animated diagrams throughout.

Appraisal (1945).—On the whole a good film and useful as a teaching aid in high schools, colleges and schools of nursing. The theory of accommodation presented is not the one commonly encountered in textbooks, although it can scarcely be considered as out of date—it is only partially correct, the main mechanical factor in the act of accommodation being entirely left out.

Availability.—National Medical and Biological Film Library ($1.00). Purchase (in Canada) from A & F Educational Film Corporation, 1434 St. Catherine St. West, Montreal 25, P.Q.

Humoral Transmission of Sympathetic Impulses—1946; Sound; Colour; 16 minutes.

Produced by Film Producers' Guild, for Imperial Chemical Industries Limited. Technical Advisers: Department of Pharmacology, Oxford University (Prof. J. H. Burn).

Description.—This instructional film, demonstrating sympathetic humoral transmission, records an experiment designed to show that nerve impulses are not transmitted electrically to smooth muscle but are carried by the release of a chemical substance (Sympathin) at the nerve endings; and further, that if such a chemical substance is released

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it is detectable by the response of a distant organ which has been rendered specially sensitive by denervation. Animated diagrams illustrate the theory, and the demonstrations are carried out on an anæsthetized cat.

Appraisal (1949).—An excellent physiological demonstration for medical students: up-to-date, accurate and clearly presented with good commentary. Recommended for medical students in the pre-clinical years, and suitable for senior medical students and other interested medical groups. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($2.25). For purchase apply to Publicity Department, Imperial Chemical (Pharmaceuticals) Limited, Fulshaw Hall, Wilmslow, Manchester, England.

Mechanisms of Breathing – 1936; Sound; B & W; 11 minutes.

Produced by Erpi Classroom Films (now Encyclopædia Britannica Films Inc.). Technical Adviser: Dr. Victor Johnson, University of Chicago.

Description.—An instructional film, demonstrating the mechanisms, functions and control of respiration.

Appraisal (1945).—Should be easily followed by an untrained audience, with a little preliminary instruction with respect to diffusion of gases and nervous mechanisms controlling muscle activity. Considered a useful teaching aid for senior elementary schools, high schools, colleges and schools of nursing, as well as for any interested group of adults or young people.

Availability.—National Medical and Biological Film Library ($1.00). Purchase (in Canada) from General Films Limited, 1534-13th Avenue, Regina, Sask.

MEDICAL FILM OF THE MONTH

A new method of selecting medical film programs is described by the Medical Film Guild of New York. This Medical Film of the Month plan gives a choice of films and showing dates, and provides for loan of one or more films on dates requested on the subscribers' own specified schedules. All films for physicians rented under this plan are postgraduate courses in the subjects covered. Choice of subjects is carried out with the co-operation of medical schools, and some of the films carry approval by national medical associations in the U.S.A. There are three distinct programs: (1) postgraduate, undergraduate, resident and intern training; (2) films for the laity; (3) training of nurses.

Films in the recent list come from the U.S.A., the Netherlands and Germany. They are obtainable in Canada, and details can be had from the Medical Film Guild Limited, 506 West 57th Street, New York 19, N.Y.

INTERNATIONAL REGISTER OF MEDICAL FILMS

L'Association Nationale des Médecins Cinéastes et des Cinéastes Scientifiques de France is supplementing its International Register of Medical Films. Directors and producers of films dealing with the medical and veterinary sciences, pharmacology, biology, etc., are kindly requested to mail a list of their films already completed or in production, to: Association Nationale des Médecins Cinéastes et des Cinéastes Scientifiques de France, 23, Boulevard de Latour-Maubourg, Paris 7ième, France.

The title of the film should be followed by the date of its production and an indication of its main technical data (gauge, type of emulsion, type of sound track, timing, language of commentary). The name and nature of meetings or organizations at which the films have been shown and awards obtained should also be stated.

The Association Nationale des Médecins Cinéastes et des Cinéastes Scientifiques de France sponsors annually, in every French city with a medical school, the *Festival International Permanent du Film Médico-Chirurgical et Scientifique.* These festivals draw an average attendance of 6000 physicians. Directors or producers of medical, surgical and scientific films wishing to have their films shown at the festival may apply to the Secretary of the Association.

Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

Cardiac Arrest and Resuscitation. Hugh E. Stephenson, University of Missouri School of Medicine, Columbia, Mo. 372 pp. Illust. The C. V. Mosby Company, St. Louis, 1958. $12.00.

From Witchcraft to World Health. S. Leff and Vera Leff. 236 pp. Illust. The Macmillan Company, New York; Brett-Macmillan Ltd., Galt, 1958. $4.50.

The Ecology of the Medical Student. Edited by Helen Hofer and Robert J. Glaser. 262 pp. Illust. Association of American Medical Colleges, Evanston, 1958. $3.00.

Emergency Surgery. Hamilton Bailey, International College of Surgeons. 1197 pp. Illust. 7th ed. John Wright and Sons Ltd., Bristol; The Macmillan Company of Canada Limited, Toronto, 1958. $32.00.

Behaviour and Physique. Introduction to practical and applied somatometry. R. W. Parnell, Warneford Hospital, Oxford, England. 134 pp. Illust. Edward Arnold Ltd., London; The Macmillan Company of Canada Limited, 1958. $4.75.

Hospital and Community. History of the Royal Melbourne Hospital. K. S. Inglis. 226 pp. Illust. Melbourne University Press, Victoria, Australia; The Macmillan Company of Canada Limited, Toronto, 1958. $5.00.

Diseases of Children in the Subtropics and Tropics. H. C. Trowell, University College of East Africa, Kampala, Uganda, and D. B. Jelliffe, Tulane University, New Orleans, La. 919 pp. Illust. Edward Arnold Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1958. $18.00.

The Comparative Anatomy and Physiology of the Nose and Paranasal Sinuses. Sir Victor Negus, King's College Hospital, London. 402 pp. Illust. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1958. $12.00.

Pediatric Methods and Standards. Edited by Fred H. Harvie, University of Pennsylvania, Philadelphia. 330 pp. Illust. 3rd ed. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1958. $4.50.

Sensitivity Reactions to Drugs. A Symposium organized by the Council for International Organizations of Medical Sciences, under the joint auspices of UNESCO and WHO. Edited by M. L. Rosenheim and R. Moulton. 230 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $8.50.

Electrolyte Changes in Surgery. Kathleen E. Roberts, Parker Vanamee and J. William Poppell. 113 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $5.00.

The Eye. A clinical and basic science book. E. Howard Bedrossian, University of Pennsylvania, Philadelphia. 340 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $12.00.

Deficiency Disease. Function and Structural Changes in Mammalia which Result from Exogenous or Endogenous Lack of one or more Essential Nutrients. Richard H. Follis, Jr. 577 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $16.25.

Amid Masters of Twentieth Century Medicine. A Panorama of Persons and Pictures. Leonard G. Rowntree. 684 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $12.75.

Guide pour l'étude de la formation à donner aux enseignants en matière d'éducation sanitaire. A Study Scheme for Training of Health Educators. 19 pp. World Health Organization, Geneva, Switzerland, 1957.

De circulatione sanguinis. The Circulation of the Blood. Two anatomical essays by William Harvey together with nine letters written by him. Translated from the Latin by Kenneth J. Franklin. 184 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $5.50.

Evolution of the Speech Apparatus. E. Lloyd DuBrul, College of Dentistry, University of Illinois, Chicago. 103 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $5.25.

Methods for Research in Human Growth. Stanley M. Garn, Fels Research Institute, Yellow Springs, Ohio, and Zvi Shamir, Hadassah-Hebrew University Hospital and Medical School, Jerusalem, Israel. 121 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $5.25.

Practical Blood Transfusion. J. D. James. 187 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $5.50.

Pain. Harold G. Wolff, Cornell University, New York and Stewart Wolf, University of Oklahoma, Oklahoma City. 121 pp. Illust. 2nd ed. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $4.75.

The Recovery Room. John Adriani and John B. Parmley, Tulane University, New Orleans, La. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $4.75.

Lesions of the Lower Bowel. Raymond J. Jackman. Mayo Clinic, Rochester. 347 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $17.00.

Temporal Lobe Epilepsy. Edited by Maitland Baldwin and Pearce Bailey, Georgetown University, Washington, D.C. 581 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $17.00.

Self-destruction. A Study of the Suicidal Impulse. Beulah Chamberlain Bosselman, University of Illinois, Chicago, Ill. 94 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $5.25.

The Amphetamines, their Actions and Uses. Chauncey D. Leake, Ohio State University, Columbus, Ohio. 167. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $5.00.

The Comparative Morphology of the Carotid Body and Carotid Sinus. William Edgar Adams, University of Otago, Dunedin, New Zealand. 272 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $11.50.

Pathologische Physiologie. Pathological Physiology. Max Buerger. 787 pp. Illust. Veb Georg Thieme, Leipzig, W. Germany, 1958. DM 54.

Preventive Medicine in World War II. Vol. IV. Communicable Diseases Transmitted Chiefly through Respiratory and Alimentary Tracts. Published under the direction of Major General S. B. Hays, The Surgeon General, United States Army. 544 pp. Illust. Office of the Surgeon General, Department of the Army, Washington, D.C., 1958.

Centaur. Essays on the History of Medical Ideas. Félix Marti-Ibanez, New York Medical College, New York. 714 pp. MD Publications, Inc., New York, 1958. $6.00.

An Atlas of Esophageal Motility in Health and Disease. Charles F. Code, Mayo Clinic, and others. 134 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $9.25.

Thirst. Physiology of the Urge to Drink and Problems of Water Lack. A. V. Wolf, Walter Reed Army Medical Center, Washington, D.C. 536 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $13.75.

Postmortale Klinisch-Chemische Diagnostik und Todeszeitbestimmung mit Chemischen und Physikalischen Methoden. Postmortem Chemical Diagnosis and Determination of Time of Death by Chemical and Physical Techniques. F. Schleyer, Bonn University. 66 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany, 1958. $3.50.

Renal Circulation in Acute Renal Failure. Ole Munck, University of Copenhagen, Denmark. 54 pp. Illust. Blackwell Scientific Publications, Oxford, England; The Ryerson Press, Toronto, 1958. $3.50.

Sherrington. Physiologist, Philosopher and Poet. Lord Cohen of Birkenhead, University of Liverpool, England. 108 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $4.25.

Social Psychiatry in Action. A Therapeutic Community. Harry A. Wilmer, National Naval Medical Center, Bethesda, Md. 373 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $9.50.

Radiation Protection. Carl B. Braestrup and Harold O. Wyckoff. 361 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $11.50.

Physiological Bases of Psychiatry. Edited by W. Horsley Gantt, The Johns Hopkins University, Baltimore, Md. 344 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $11.50.

Diseases of the Liver and Biliary System. Sheila Sherlock, University of London, England. 719 pp. Illust. 2nd ed. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $13.75.

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References to books should be set out as follows:

PICKWICK, S., *Textbook of Medicine*, Jones and Jones, London, 1st ed., p. 30, 1955.

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RADIOLOGIST, age 38 years, Europe and U.S.A. trained, also neuroradiology, references, writing certification examinations fall 1959 and L.M.C.C. next May, seeks hospital position preferably in the Maritimes. Write to Box 956, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

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CANADIAN GRADUATE, two years' training in internal medicine, desires position as assistant to practitioner or group in southern Ontario general practice. Married. Available August 1959. Reply to Box 113, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

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MEDICAL NEWS *in Brief*

(Continued from page 297)

TREATMENT OF POST-IRRADIATION HÆMATOPOIETIC DEPRESSION

The techniques of freezing bone marrow in glycerin under regulated conditions of refrigeration permits the preservation of marrow cells in a viable state for long periods of time. Kurnick and his colleagues (*Ann. Int. Med.*, 49: 973, 1958) utilized this method in collecting and preserving bone marrow from patients who are to receive intensive courses of radiotherapy in the treatment of malignant conditions. The theory behind this procedure is that the reinfusion of such autogenous material would result in an effective implantation, since no heterogeneous material would be included. The initial experience of the writers with this method of marrow replacement after depression of the bone marrow following radiation is described in two patients who received such treatment. The cells were preserved in solidified carbon dioxide for 14 days to two months, while the patients received radiotherapy with an average tissue dose of 2000 r. The marrow, preserved in glycerol, was diluted and reinstilled intravenously after the completion of radiotherapy. Serial examinations of the bone marrow revealed that the marrow — initially extremely hyperplastic as a result of the radiation depression — was progressively reconstituted in all cases. Within two weeks the marrow could be made hyperplastic. The experience with patients suffering considerably lesser degrees of hæmatopoietic depression by irradiation indicates that such rapid re-establishment of marrow cellularity is, under ordinary circumstances, extremely unusual. However, in the three observations reported, it was not possible to exclude the occurrence of spontaneous re-establishment, even though such an explanation is highly improbable. Surgical intervention had no adverse effect. Unhappily, both these patients succumbed at a later date to their neoplasms. At the same time as that of the present report, two similar experiences were observed in additional patients.

The method of collection and preservation of bone marrow before hæmatopoietic depression should be applicable primarily in patients with potentially curable neoplasms, even in patients with metastases, if rapid and extensive radiotherapy is considered to be indicated. It is even suggested that this method could be applied in patients who are to have treatment with chemotherapeutic agents characterized by a depressive effect on the bone marrow. In normal subjects to be exposed to the risk of excessive radiation of a non-therapeutic type, the collection and preservation of bone marrow might possibly be of value in rapidly developing urgent situations.

VENTRICULAR SEPTAL DEFECT IN INFANTS AND CHILDREN

A series of 98 patients (median age 6 years) with ventricular

septal defects demonstrated by cardiac catheterization were studied in detail by Fyler *et al.* (*Circulation*, 18: 833, 1958) with respect to clinical and catheterization data.

The various sub-groups — uncomplicated small left-to-right shunts, uncomplicated large left-to-right shunts, associated pulmonic stenosis, associated pulmonary vascular disease, associated aortic regurgitation — presented a series of physiological findings with gradual transitions between the sub-groups. Nevertheless, in the majority of cases, the sub-group was clinically recognizable.

The electrocardiogram provided important information about the physiological diagnosis; it was even useful in selecting patients who might benefit from surgical treatment. For example, in the absence of clinically recognizable pulmonic stenosis, right ventricular hypertrophy virtually excluded the possibility of surgical intervention. Along the same lines, left ventricular hypertrophy occurred almost exclusively in those who were good candidates for surgical intervention. In patients with combined ventricular hypertrophy catheterization was required in order to determine whether surgical intervention was possible without excessive operative risk.

The period of follow-up varied from one to 13 years (median: 5 years) in approximately 50% of the cases. No sign of the development or augmentation of pulmonary vascular disease was noted in this group of children. Late clinical deterioration was noted principally in those with large left-to-right shunts without pulmonary vascular obstruction or pulmonic stenosis.

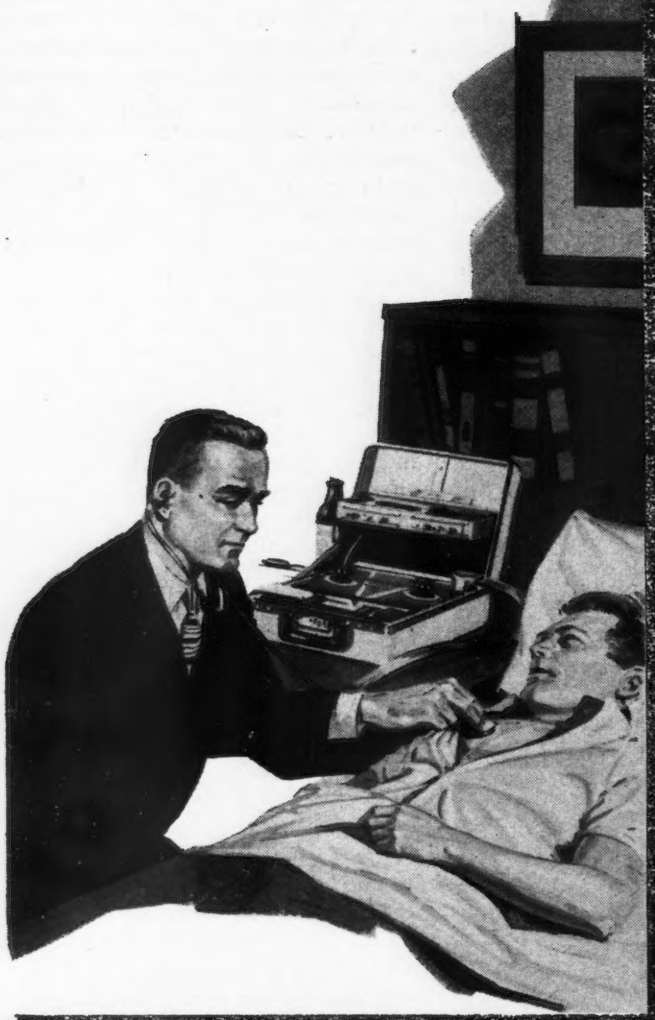
The prognosis in children with ventricular septal defects is apparently good for several years after infancy. Only one patient died as a result of his ventricular septal defect in this series of 98 children catheterized.

TRACHEAL FENESTRATION IN THERAPY OF CHRONIC PULMONARY DISEASES

Tracheal fenestration combined with effective tracheobronchial aspiration and medication constitutes a new hope for the respiratory cripple, according to Rockey (*Am. Rev. Tuberc.*, 78: 815, 1958). With the help of repeatedly inserted special suction catheters, the evacuation of the tracheobronchial tree is considered to be more thorough than it would be by expectoration, and it constitutes no effort for the patient. The beneficial palliative effect of tracheal fenestration on three moribund patients is described and the results are considered to justify the additional clinical application of this technique.

In contrast to tracheotomy, tracheal fenestration maintains a normal air tract, and therefore, does not interfere with phonation or with the cough mechanism. The surgically created tracheo-cutaneous fistula is closed at all times except when the skin valves are held apart. It is lined with skin, and there is therefore no need to keep its surfaces apart by a cannula in

(Continued on page 60)



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MEDICAL NEWS *in brief*

(Continued from page 55)

order to prevent re-growth or obliteration. The easy insertion of a catheter or bronchoscope through the fenestration opening permits repeated endobronchial observation and medication, and the effect of various test materials on the bronchial mucosa can be studied.

The indications for tracheal fenestration are: advanced emphysema with or without suppuration; suppurative diseases of the lungs, when excisional surgery is contraindicated; far advanced pulmonary tuberculosis, for which no other form of therapy can be devised; fibrocystic disease of the pancreas with gross pulmonary suppuration; and bulbar poliomyelitis with irreversible changes requiring a mechanical respirator.

FAILURE OF ISOLATION TECHNIQUES TO HALT HOSPITAL INFECTION

In a Milwaukee hospital, Koch and his colleagues (*J.A.M.A.*, 169: 99, 1959) tried to evaluate the possible benefit of simple semi-isolation techniques as a means of controlling the spread of cross-infection. They took two 60-bed general surgery wards and treated one as an isolation ward with special bedding, dressing cart, utensils and hand-washing facilities, while personnel wore caps, gowns, masks and gloves and used strict aseptic techniques in dealing with dressings; the other ward was simply used as a control and subjected to routine hospital methods. In spite of this, during a period of one year, 41 of the 74 patients who acquired a hospital infection with coagulase-positive phage-typable staphylococci did so on the isolation ward, as against 33 on the control ward. Of cases of cross-infection, 24 were located on the isolation ward and 18 on the control ward. Carrier rates among staff were almost the same —34 and 38% in the two wards.

An attempt was made to decrease resistance of staphylococci by withdrawing the use of tetracycline drugs for periods of eight months, but this had no effect on the rate of incidence of recovery of resistant strains. This disappointing result may be due to

(Continued on page 62)

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venous infusion of homologous marrow cells one or two days after the exposure to radiation. The infused marrow cells migrate to their appropriate sites in the medulla of the irradiated subject, divide, multiply, and aid in restoring medullary function in time to save the life of the subject.

In recent studies, selected patients with leukæmia received considerable doses of irradiation of the whole body (200 to 600 r) and an infusion of normal bone marrow from appropriate cadavers or volunteers. In certain cases, remission of the leukæmic process of significant degree and duration followed these measures. In other cases, the patient experienced only temporary benefits. An obvious consideration in predicting the result of such treatment is the dose of irradiation used and the relative radio-resistance of the leukæmia in question. A type of resistant leukæmia that requires, for example, a greater dose of irradiation than the intestine can stand would not be greatly benefited by a dose of 200 or 300 r to the tissues, combined with a small quantity of bone marrow. Even in laboratory animals, greater doses of irradiation — i.e., doses of 800 to 1000 r — are required for the production of a successful permanent marrow homograft or a useful effect on the leukæmia.

In rodents with inadequate irradiation, marrow grafts are temporary, but the marrow of the host regenerates. When the irradiation is adequate, the graft is permanent and the marrow of the host does not regenerate. Between the two — in the vicinity of 500 r in rodents and dogs—neither the marrow of the host nor the medullary graft succeeds adequately, and in this situation the mortality is high. In man, the critical dosage should be in the vicinity of 500 r, but this has not been clearly defined.

In subjects with adequate irradiation, the marrow graft can "take", although death supervenes because of the presence of intercurrent infection with a relatively aplastic lymphoid system. Therefore, infusions of marrow in such cases have apparently restored the marrow of the subject, but have not necessarily restored the func-

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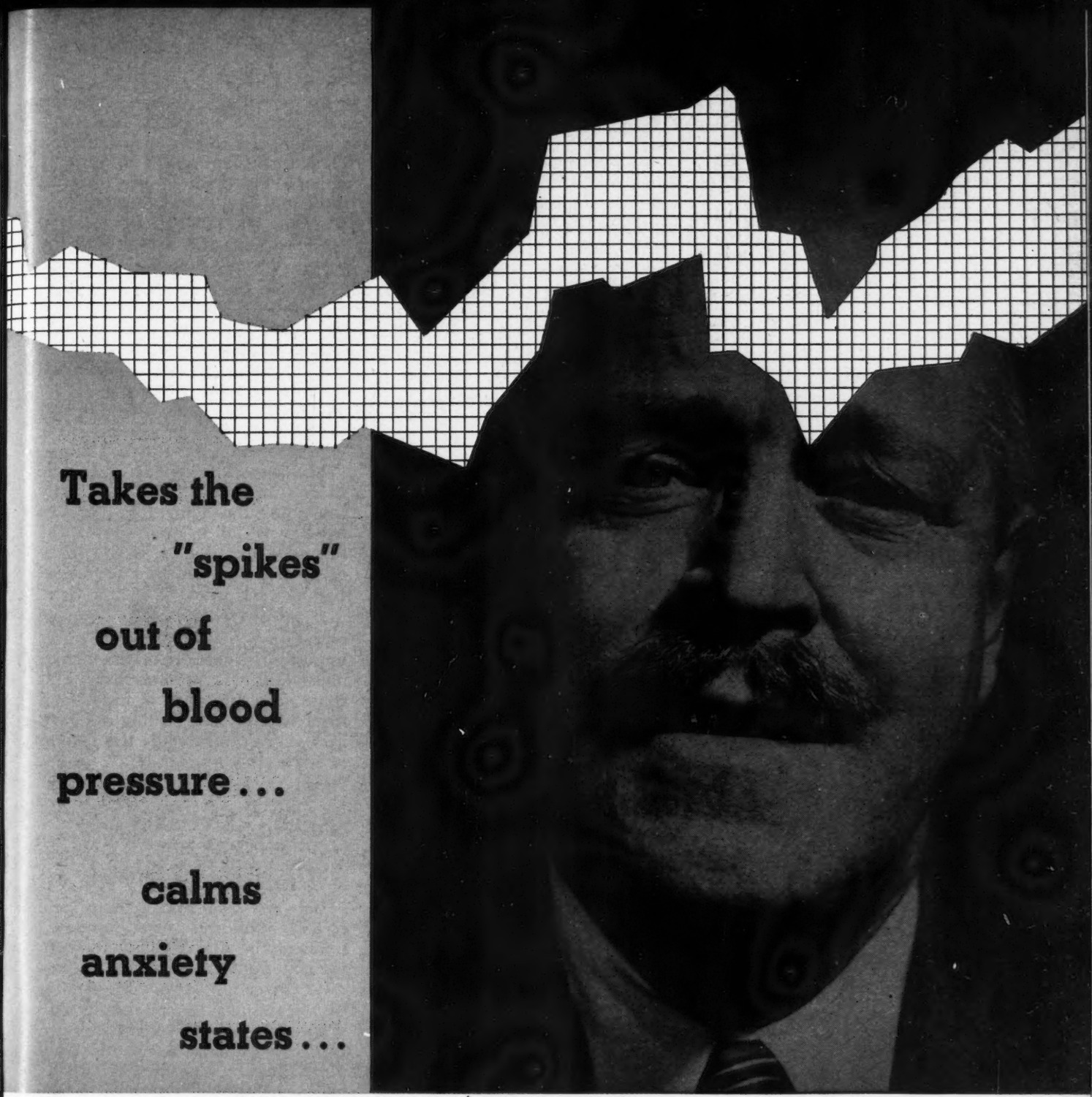
the widespread use of such drugs outside the hospital (to such an extent that 33% of strains of staphylococci on admission are resistant to them).

The authors draw attention to the importance of the fæcal carrier; fæces was the sole source of staphylococci in 31% of all carriers detected. Little evidence was found to support the view that inpatient nasopharyngeal carriers are a potential source of cross-infection; on the other hand, patients with open skin lesions represent a real hazard.

RADIATION INJURY AND MARROW REPLACEMENT

The exposure of the entire body to ionizing radiation of the order of 500 to 1000 r is followed by death of the subject in 7 to 10 days. Marrow dysfunction is the primary cause of such deaths, and the symptoms are primarily bleeding and septicæmia. In many species of animals, this type of death can be avoided by the intra-



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MEDICAL NEWS *in brief*

(Continued from page 62)

tion in the irradiated spleen and lymph nodes. A possible remedy has been proposed in the form of additional injection of fetal lymphoid tissues. It is possible that further investigation of this procedure will be of value. The major problem – i.e., the restoration of the lymphoid defences and the treatment of infection in the irradiated subjects – requires additional investigation.–J. W. Ferrebee and E. D. Thomas, *Ann. Int. Med.*, 49: 987, 1958.

ORAL OR INTRAMUSCULAR IRON?

Yu and his colleagues from Brooklyn (*J. Pediat.*, 54: 50, 1959) made a comparison of intramuscular iron-dextran complex and oral ferrous sulfate in the treatment of iron-deficiency anæmia in children with hæmoglobin values of less than 8.5 g. %. The iron-deficiency anæmia in this series was nutritional in origin in all but one little girl with hookworm infestation; most of the patients were aged three months to four years.

In the series given intramuscular iron-dextran complex (Imferon), the children were given injections of 50 to 100 mg. (1 to 2 ml.) either daily or at longer intervals until the total calculated dose was reached. The other group received an elixir of ferrous sulfate by mouth in daily dosage of 0.6 g.

Where the anæmia was uncomplicated, intramuscular therapy gave average gains of 2.1 and 2.2 g. % in the first and second weeks; where it was complicated by infection the figures were 1.8 and 1.7 g. %, and where it was complicated by lead poisoning the figures were 0.7 and 1.3 g. %. When a weekly injection schedule was substituted for the daily schedule, the gain for the first week was 1.4 g. % and for the second week 2.3 g. %. In the group given oral iron, the gain was about 1 g. % each week.

It appears that where a rapid elevation of hæmoglobin level is important, injection of iron intramuscularly is preferable. This route also provides a faster and surer way of replenishing depleted iron stores, and avoids the hazard of a careless mother.

SURGICAL CORRECTION OF CONVERGENT STRABISMUS (Esotropia)

Between 1950 and 1956, a total of 350 children were operated upon at the Mayo Clinic for convergent squint. Because the surgical correction of convergent strabismus, especially in young children, is a controversial subject, Dyer and Martens (*Proc. Staff Meet. Mayo Clin.*, 33: 658, 1958) made a follow-up survey of the results in 176 of this series.

In 20 of these patients there had been a possible precipitating factor for the squint; three had had some birth injury, six an accident, 10 a febrile illness and one an immunization. In 33 cases there was a positive family history of squint. Only 21 of the patients were amblyopic at the time of operation. Operation was not performed on any patient under two years of age, and the follow-up ranged from six months to six years. Refractive errors vary between plus 2 and 4 dioptres in the majority of cases; where the amount of esotropia was great, unusual muscle

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MEDICAL NEWS *in brief*
(Continued from page 64)

adhesions and check ligaments were often noted at operation.

The recession-resection operation was used in the majority of cases, and resulted in a substantial number of satisfactory and good functional results with minimal undesirable postoperative effects. The incidence of functional improvement was highest in patients with less than 40 dioptres of deviation, in patients whose esotropia began at three to four years, in patients with a squint of less than one year's duration. In patients with a squint present at birth, results were best within a range of four to five years. The age at which operation was performed did not appreciably affect the end results.

FIRST INTERNATIONAL MEDICAL CONFERENCE ON MENTAL RETARDATION

The First International Medical Conference on Mental Retardation, organized by the Maine Chapter of the American Academy of Pediatrics, the Division of Maternal and Child Health, Maine Department of Health and Welfare, and the Pineland Hospital and Training School, Pownal, Maine, will be held from July 27 to 31, 1959, at the Eastland Hotel, Portland, Maine.

The program will include in its five days of general sessions addresses on brain anatomy, the reticular system, head anomalies, phenylketonuria, lipoids, birth injury, embryology, infections, mongolism, erythroblastosis, therapy, psychiatry, psychology, and behaviour disorders. The conference is open to all physicians and has therefore been timed to follow immediately after the International Pediatric Congress in Montreal.

The tentative program, including registration and reservation forms, will be available shortly. Further information from Dr. Ella Langer, State of Maine Department of Health and Welfare, Augusta, Maine, U.S.A.

MEDICAL WRITERS' INSTITUTE

The Second Annual Medical Writers' Institute will be held on Monday, June 15, to Wednesday, June 17, 1959, at Rensselaer Polytechnic, Troy, New York. The program will be directed by Professor Jay R. Gould of R.P.I., coauthor of two well-known technical writing texts, *Technical Reporting* and *Exposition: Technical and Popular*. Coordinator will be Dr. Joseph F. Montague, prominent medical writer and lecturer, and president of the New York Chapter of the American Medical Writers' Association.

The 1959 Writers' Institute will follow the same general plan as last year with more concentration on workshop problems. Speakers will give advice on medical reports, instructions and circulars, advertising and medical journalism. Inquiries should be addressed to Professor Jay R. Gould, Rensselaer Polytechnic Institute, Troy, New York.

OLD MASSIVE EMBOLISM

An incidence of old pulmonary embolism of 1.7% (68 cases) in 4000 necropsies in a Swiss centre demonstrates that this is not a very rare condition. Of these 68 cases, Zollinger and Hensler (*Schweiz. med. Wchnschr.*, 88: 1227, 1958) were able to follow up thoroughly 14 cases, and they present four case reports as typical examples of the clinical picture of old massive pulmonary embolism. Only in three of these 14 cases was the presumptive diagnosis of pulmonary embolism made; in the remaining cases, various forms of heart failure were blamed for the fatal outcome. The history rarely contained any suggestion of thrombophlebitis or pulmonary infarction, but sometimes there was a past history of paroxysms of nocturnal dyspnœa or sudden pleuritic pain or hæmoptysis. Retrosternal pain with radiation to the back or shoulders was commoner and probably an expression of coronary insufficiency due to pulmonary hypertension. The right ventricle was usually enlarged, the second pulmonary tone was accentuated or split, there was a systolic murmur over the pulmonary valve and in advanced cases a Graham-Steell murmur could be heard. The ECG showed a right ventricular hypertrophy pattern in seven of the cases, and in five there was a vertical heart pattern, and in two a left-sided pattern.

(Continued on page 78)

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1. Traylor, J. B., and Torpin, R.: Am. J. Obst & Gynec. 61:71 (Jan/51)
2. Guest, G. M., & Brown, E. W.: A. M. A. Am. J. Dis. Child. 93:486 (May/57)

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MEDICAL NEWS *in brief*

(Continued from page 76)

The radiological features typical of pulmonary embolism, i.e. increased density of one or both pulmonary arteries, were present in 11 of the cases.

The differential diagnosis includes pulmonary artery thrombosis, atrial septum defect and pulmonary stenosis. Old venous thrombosis in the deep veins of the thigh was found in 57 cases. In five cases where no other thrombi were present, right atrial thrombosis was found. The disease responsible for peripheral thrombosis or thrombosis in the right atrium was arterial hypertension (15 cases), carcinoma (13 cases), cerebral arteriosclerosis (9 cases), myocardial degeneration (10 cases), myocardial infarction (7 cases), pulmonary tuberculosis (5 cases), mitral stenosis (2 cases), trauma and operation (2 cases each), endocarditis (one case), epilepsy and prostatism (one case each).

FIRST INTERNATIONAL CONGRESS OF ENDOCRINOLOGY

The First International Congress of Endocrinology will be held in Copenhagen, Denmark, July 18 to 23, 1960. The president will be Professor Bernardo A. Houssay of Argentina, and the International Executive Committee contains many noted endocrinologists. The Congress will be preceded by the Fourth International Goitre Conference, to be held in London, England, from July 5 to 9, 1960.

The official languages for the First International Congress of Endocrinology will be English, French, German and Spanish. The preliminary program contains ten symposia on C.N.S. regulation of anterior pituitary secretion, polypeptide anterior pituitary hormones, posterior pituitary hormones, parathyroid hormone and calcium metabolism, aspects of reproduction, adrenocortical syndromes, aldosterone, steroid pharmacology, hormone action at the cellular level, and topics in comparative endocrinology. There will be a round table discussion of hormone assays of clinical value, and a series of short communications and discussions. Scientific and technical exhibitions will be arranged in the congress building, the Technical University of Denmark. Information from the Congress Secretariat, Hormone Department, Statens Seruminstitut, Copenhagen S, Denmark.

PERCUTANEOUS PROSTATIC BIOPSY

A Melbourne surgeon, Macleish (*Australian & N.Z. J. Surg.*, 28: 141, 1958), defends the use of needle biopsy for the diagnosis of carcinoma of the prostate. He describes his technique for prostatic biopsy under local anæsthesia, the Turkel needle being inserted 3 cm. anterior to the anus and directed with finger guidance from the rectum into the prostate.

In the past five years 35 biopsies have been attempted by this method; in five, no prostatic tissue was obtained. In 19 cases the tissue obtained showed normal prostate, in eight it showed carcinoma and in three it showed calculous prostatitis. There were no cases of

urinary extravasation or infection after this procedure, and only two small hæmatomas appeared in the perineum. The method is contraindicated in the presence of an infection, osteoarthritis preventing hip flexion and metastatic disease.

A NEW BASIC SCIENCES PUBLICATION

The Canadian Federation of Biological Societies, which was founded in 1958 as a federation of the Canadian societies representing anatomy, biochemistry, pharmacology and physiology, now has its own publication. The first issue of *Canadian Federation News (Bulletin de la Féderation Canadienne)* recently appeared under the editorship of Dr. P. G. Scholefield of Montreal. This periodical is designed as a medium for the exchange of news and views between members of the four constituent societies, and not primarily as a medium for the publication of scientific articles. Nevertheless, the first issue (whose costs were underwritten by Geigy Pharmaceuticals) contains a scholarly article by Dr. Maclaren Thompson on the forgotten physiologist, Wharton Jones, who had a considerable influence on Thomas Huxley and also on Lister. There is an article in French contributed by Dr. Pierre Jobin on the new Medical School of Laval University. The bulk of the periodical is, however, concerned with news of the Federation's activities and of other activities in the basic sciences in Canada and abroad.

This first issue is well produced and well edited, and it is to be hoped that funds will be forthcoming for the underwriting of future issues.

RAEDER'S PARATRIGEMINAL SYNDROME

A syndrome consisting of drooping of the eyelid and a contracted pupil with headache but without loss of sweating on the face was described by Raeder in 1924. Ford and Walsh (*Bull. Johns Hopkins Hosp.*, 103: 296, 1958) have observed more than 25 cases of this syndrome in recent years. The headache begins early in the morning, often ceases about noon, and may persist for weeks or even months. The onset is in middle age or old age, and males seem to be more frequently affected. This syndrome is benign but its cause has never been established. No aneurysm was ever demonstrated by the authors, nor have they ever seen a case develop subarachnoid hæmorrhage. As careful questioning elicited without exception a history of migraine type of headaches in the past, the authors believe that this syndrome is merely an unusual result of severe and frequent migrainous headaches. According to them, the condition is a stereotyped one, and they present one case history which can be considered typical of all their cases.

ANTIHISTAMINE TREATMENT OF SEVERE BURNS

Histamine has long been considered an important factor in the pathogenesis of shock, and attempts have therefore been made

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from time to time to use antihistaminic drugs to counteract shock in such cases as severe burns. However, the effects of antihistamine therapy have usually been regarded as negligible. Birke and his colleagues from Stockholm (*Acta chir. scandinav.*, 115: 401, 1958) report a further study of the effect of antihistamine (promethazine) treatment on the urinary excretion of histamine catechol amines and corticosteroids, as well as on elimination of dextran and serum albumin, in nine cases of severe burns. Like other observers, they found no effect on the levels of histamine in blood and urine from the treatment. Moreover, the elimination of dextran and serum albumin was within the same range in the antihistamine-treated cases and in controls. However, they did note a significantly lower excretion of corticosteroids on the second to fifth day in the series treated with promethazine, and suggest that this may indicate less pronounced stress and a favourable effect of antihistamine in severe burns. They also mention that the patients treated with promethazine behaved more calmly and were less affected by pain. The series is, however, too small to permit firm conclusions.

MALARIA ERADICATION

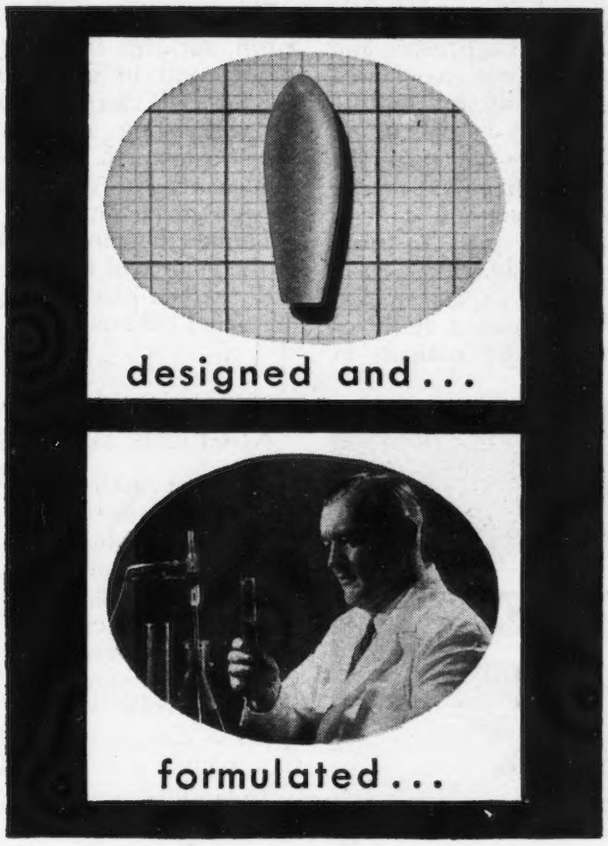
The World Health Organization has produced a small pamphlet entitled "Malaria Eradication: A Plea for Health". In a foreword the Director of W.H.O., Dr. M. G. Candau, emphasizes that eradication of malaria in the world has become a reality which is within our reach, but that the success or failure of this important undertaking depends on the extent to which more privileged members of the world community support it and on the timeliness of that support. Because of the steadily increasing resistance of malaria vectors to insecticides, such an eradication program has become extremely urgent. The pamphlet then reviews some of the facts which have led W.H.O. to inaugurate its policy of malaria eradication on a global basis.

AWARDS FOR MANUSCRIPTS ON OBSTETRICS AND GYNÆCOLOGY

The Division of Obstetrics and Gynecology of the International College of Surgeons has announced its second annual competition for two awards for the best manuscripts on a phase of obstetrics and gynæcology. The first award will be $500 and the second $300. The contest is limited to (1) interns, residents, or graduate students in obstetrics and gynæcology, or (2) those engaged in the practice or teaching of the specialty. Contestants must hold a degree of medicine from an accredited college of medicine. Fellows of the International College of Surgeons are not eligible.

Manuscripts of not more than 5000 words must be submitted on

(Continued on page 84)



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or before June 1, 1959, to Dr. Harvey A. Gollin, secretary of the prize committee, 55 East Washington Street, Chicago 2. For information on contest rules, write to Dr. Gollin.

NUCLEAR SEX AND TUMOURS OF TESTES

It has previously been noted that in tumours of the testes cells of "female" nuclear sex are often present. It has also been claimed that testicular tumours are much commoner in maldescended testes, and that certain ones are associated with the pseudohermaphrodite state. The question has therefore arisen whether the cells of the hosts of testicular tumours may also show "female" nuclear sex.

At the Armed Forces Institute of Pathology, Washington, D.C., Ashley and Theiss (*Science*, 128: 1434, 1958) undertook a study of the nuclear sex of 75 patients in whom testicular tumours of all types had developed. Sections were stained by hæmatoxylin and eosin and by the Feulgen technique, and in each instance the Leydig cells, Sertoli cells, and cells of supporting connective tissue were examined. In all cases the nuclear sex was diagnosed as male, though seven out of 25 teratomas contained female elements. Hence in the genesis of testicular tumours, little part is played by gross error of sexual differentiation.

TRAINING COURSE IN NUCLEAR MEDICINE

By joint action of the North-Eastern Chapter of the Society of Nuclear Medicine, the University of Montreal and the Montreal General Hospital, a training course in nuclear medicine for physicians has been arranged and is timed to start late in March and continue for two weeks (6 days a week; 6 hours a day, 2-10 p.m.). A long-term course will follow in 1959-60.

Theoretical and practical tests will be given at the end of the course. Successful students will receive a certificate issued by the teaching committee of the Society of Nuclear Medicine. A list of successful candidates will be sent to the Radiation Services of the Department of National Health and Welfare, to serve as a requirement for the licence to use radioactive isotopes; however, this does not imply an automatic approval of the licence.

The tuition fee is $100.00. A limited number of scholarships will be available.

Application should be made, by February 28 if possible, to Dr. Joseph Sternberg, Society of Nuclear Medicine, North-Eastern Chapter, University of Montreal. The course is limited to 20 students. If the number of applicants exceeds this limit, another condensed course will be arranged later in the year.

Outline of course. – Emphasis will be placed on the practical aspects of nuclear medicine; each student will be required to perform personally the laboratory and clinical procedures. Students who follow simultaneously the theoretical course at McGill University or those who possess a certificate from previous years are not required to

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attend the review of fundamental data; however, it is advisable for them to refresh their knowledge in this matter.

I. Review of the fundamental data necessary for the practice of nuclear medicine. Duration: 10 hours. The lectures will cover the definition and principles of radiation, interaction of radiation with matter, means of detection of radiation, statistics of counting, interpretation of results, limitations and errors, and the biological action of radiation.

II. Handling of equipment in nuclear medicine. Duration: 20 hours. The student will learn the use of Geiger counters and other instruments. The notions of half-life and energy, self-absorption and the geometry of counting and errors will be discussed. Demonstrations will be presented of topographical and time scanning procedures *in vivo*. Radiochemical techniques and experimental procedures will be demonstrated.

III. Physiological bases of the use of radioisotopes in medicine. Duration: 20 hours.

IV. Clinical use of radioactive isotopes. Duration: 30 hours. Thyroid uptake procedures, hæmatological procedures, and therapeutic applications of radioisotopes will be demonstrated and discussed.

ARTERIOGRAPHY AND SOME NEW CONCEPTS OF CORONARY HEART DISEASE

Because they had developed a technique for direct bypassing of experimental coronary occlusion, Thal and his colleagues, of Minneapolis, had to devise an objective method of demonstrating coronary occlusion in the human before attempting operative intervention. This they have achieved by means of arteriography with biplane films taken at 6 per second after injecting 90% diatrizoate through an intra-aortic catheter. The technique produced good results in over 50 studies described in a report in the *J. A. M. A.* (168: 2104, 1958). Both normal and abnormal radiographs are presented by these authors, and four case histories show the value of arteriography in certain cases. Their studies forced the authors to conclude that their original premise that coronary occlusion is usually restricted to the proximal portions of the main coronary arteries, was erroneous. Patients with angina pectoris on effort usually had diffuse disease of the whole coronary tree, and those with angina at rest had additional impairment of the collateral circulation. This would make the value of bypass grafting more than doubtful. In only two of their cases was segmental occlusion found, and both these patients were free of symptoms.

Claude S. Beck and his coworkers in Cleveland (*J. A. M. A.*, 168: 2110, 1958) believe that the most common cause of death in coronary artery disease is self-electrocution of the heart when there is uneven distribution of blood. These hearts are often anatomically too good to die, for there may not even be an infarction or occlusion, but only a narrowing. In preventing such fibrillating currents from developing they believe that their opera-

tion, designed to develop good intercoronary communication, has been of proved value. The Beck operation consists basically of gentle abrasion of the epicardium between the branches of the arteries and light application of freshly prepared trichloracetic acid (5% aqueous solution) to the abraded area. In addition, the coronary sinus is narrowed to a diameter of 3 mm. by a silk ligature, and finally powdered asbestos is sprinkled on the surface of the heart. Although they have performed this operation in 100 consecutive cases without a death, the authors admit that if cases of severe inflow restriction are selected there will be some mortality. But such patients have a limited expectancy anyhow and stand to benefit a great deal if they survive the operation, which can be modified to minimize the risk in cases where the heart is extremely irritable. The Beck operation was performed on 347 patients in the period between January 1954 and February 1958. One-third of the patients had advanced disease (salvage operations). Among them the hospital mortality was 11% and subsequent mortality 15%. Among the non-salvage cases the hospital mortality was 3%, and the subsequent mortality during the four-year period was 7%, for a total of 10%. This record emphasizes the desirability of early operation, which is specially designed to prevent death through electric imbalance of the myocardium. Of the surviving 295 patients, 94% have obtained an excellent or a good result, many have been able to return to gainful occupations, and almost all have an increased capacity for work. Many patients have stated that their feet have been much warmer since the operation, and this has been confirmed by actual temperature measurements before and after operation in 23 cases (rises as high as 10° C. have been observed). Many patients state that their entire body is warmer and some that their memory is better. A radial pulse in the left arm which had been absent since an occlusion one year earlier reappeared two days after this operation. In 17 out of 20 patients with distressing arrhythmias, these either completely disappeared or diminished in severity and frequency.

NINTH INTERNATIONAL CONGRESS OF RADIOLOGY

The Ninth International Congress of Radiology will take place in Munich from July 23 to 30, 1959, under the patronage of the president of the West German Republic, Professor Heuss. The Congress will be associated with a scientific exhibition and a technical exhibition, and the main subjects for plenary sessions include television in radiology, preoperative irradiation of malignant tumours, radiation damage to the population through the medical use of x-rays, automation in diagnosis, effects of x-rays on cell metabolism, chemical and biological protection against radiation, and present problems in radiology. Sectional meetings will deal with diagnostic and therapeutic problems, and subjects for discussion will include problems of nuclear medicine, problems in radiation biology and biophysics, and legal problems in radiology. Further information from the Congress Secretariat, Professor J. Ries, Munich 22, Reitmorstrasse 29, W. Germany.